Investigating the clinical correlates of violent behaviour in schizophrenia

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INVESTIGATING THE CLINICAL CORRELATES OF VIOLENT BEHAVIOUR IN SCHIZOPHRENIA

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Abstract

Background

There is an association between schizophrenia and violence, although the specific drivers for this link remain unclear. This study aimed to explore the relationships between childhood adversity, conduct disorder, substance misuse and violence among men with schizophrenia. It has been suggested that there may be different pathways to violence in schizophrenia, one primarily linked with pre-morbid conduct disorder, so patients were specifically grouped on the basis of pre-morbid conduct disorder.

Methods

Ninety-three male participants were recruited for the study, fifty-four with schizophrenia and thirty-nine healthy controls. Participants underwent a range of clinical assessments, including symptoms of conduct disorder, exposure to childhood adversities and history of substance use disorders. Adult propensity to violence was measured using the Gunn Robertson Violence Scale. Those participants who consented also had a structural magnetic resonance imaging scan.

Results

The Gunn Robertson Violence Scale has good validity in this population. Conduct disorder was associated with an increased propensity to violence. Exposure to domestic violence during childhood and the cumulative number of childhood adversities were both associated with adult propensity to violence and attenuation of the association with cumulative adversities suggested that conduct disorder may be a mediator of the relationship. Patients with pre-morbid conduct disorder began using alcohol and cannabis earlier and more frequently, and had higher rates of lifetime substance use disorders which were associated with an increased propensity to violence. An increase in grey matter volume in the caudate was correlated with an increased lifetime propensity to violence.

Conclusions

Conduct disorder, substance use disorders, childhood adversity, schizophrenia and violence are all associated with each other. Hence there is a complex interplay of factors, with their origin in childhood, which increase the risk of violent behaviour in schizophrenia.

Table of Contents

ABSTRACT 2

TABLE OF CONTENTS 4

TABLE OF FIGURES 11

TABLE OF TABLES 12

ACKNOWLEDGEMENTS 13

STATEMENT OF CONTRIBUTION 14

ABBREVIATIONS 15

CHAPTER 1 INTRODUCTION TO SCHIZOPHRENIA 16

1.1 ABSTRACT 16

1.2 BACKGROUND 16

1.3 DIAGNOSIS 17

1.3.1 Positive symptoms 17

1.3.2 Negative symptoms 18

1.3.3 Cognitive deficits 19

1.3.4 Clinical subtypes 19

1.3.5 Operationalized diagnosis 19

1.4 EPIDEMIOLOGY 20

1.5 AETIOLOGY 21

1.5.1 Genetics 21

1.5.2 Environment 23

1.6 MANAGEMENT 25

1.6.1 Pharmacological 25

1.6.2 Psychological 26

1.7 SUMMARY 27

CHAPTER 2 SELECTIVE REVIEW OF THE LITERATURE RELATING TO SCHIZOPHRENIA AND VIOLENCE 28

2.1 ABSTRACT 28
2.2 BACKGROUND 28
2.3 PSYCHOTIC SYMPTOMS 29
2.3.1 Positive psychotic symptoms 30
2.3.2 Anger 31
2.3.3 Treatment 32
2.4 CONDUCT DISORDER, ANTISOCIAL PERSONALITY DISORDER AND PSYCHOPATHY 32
2.4.1 Conduct disorder 32
2.4.2 Antisocial personality disorder 33
2.4.3 Psychopathy 33
2.5 SUBSTANCE MISUSE 34
2.5.1 Substance misuse and conduct disorder 34
2.6 CHILDHOOD ADVERSITY 35
2.6.1 Childhood adversity and conduct disorder 35
2.7 GENETICS 36
2.7.1 Search strategy 36
2.7.2 Monoamine oxidase 36
2.7.3 Catechol-O-methyltransferase 36
2.8 IMAGING 38
2.8.1 Search strategy 38
2.8.2 Structural imaging 38
2.8.3 Functional imaging 41
2.8.4 Implications 43
2.9 CHALLENGES OF RESEARCH INTO VIOLENCE AND SCHIZOPHRENIA 44
2.9.1 Violence definition 44
2.9.2 Co-morbidities 44
2.10 TYPOLOGIES OF VIOLENCE IN SCHIZOPHRENIA 45
2.11 SUMMARY 45
CHAPTER 3 QUANTIFYING VIOLENCE IN MENTAL HEALTH RESEARCH 47

3.1 Introduction to published paper 47
3.2 Validity and reliability of tools 55
3.3 Conclusions 56
CHAPTER 4 METHODOLOGY 57
4.1 Abstract 57
4.2 Aims 57
4.3 Ethical approval 57
4.4 Power calculation 58
4.5 Participants 58
4.5.1 Inclusion criteria 58
4.5.2 Exclusion criteria 59
4.5.3 Recruitment 59
4.6 Clinical assessments 60
4.6.1 Schizophrenia 60
4.6.2 Conduct disorder, antisocial personality disorder and psychopathy 61
4.6.3 Alcohol and drugs 61
4.6.4 Childhood adversity 62
4.6.5 Other clinical information 62
4.7 Assessment of violence 64
4.7.1 MacArthur Community Violence Instrument 64
4.7.2 Additional questions 65
4.7.3 Gunn Robertson Violence Scale 66
4.7.4 Buss Perry Aggression Questionnaire 66
4.7.5 Official records 67
4.8 Procedure 69
4.9 Statistical analyses 70
4.9.1 Between group comparisons 70
4.9.2 Analysis of violence 70
4.9.3 Co-linearity 70

4.9.4 Effect size 71
4.9.5 Mediation analyses 71
CHAPTER 5 CONDUCT DISORDER AND QUANTIFICATION OF VIOLENCE 72
5.1 ABSTRACT 72
5.2 BACKGROUND 72
5.3 HYPOTHESES 74
5.4 SPECIFIC METHODOLOGY 74
5.5 SPECIFIC STATISTICAL ANALYSES 75
5.6 RESULTS 75
5.6.1 Inter-rater reliability 75
5.6.2 Adjustment for confounders 75
5.6.3 Demographics 76
5.6.4 Group comparisons of clinical characteristics 78
5.6.5 Group comparison of behaviours from the MacArthur Community Violence Instrument 81
5.6.6 Group comparison of Gunn Robertson Violence Scale ratings 82
5.6.7 Validity of the Gunn Robertson Violence Scale as a measure of lifetime propensity to violence 82
5.6.8 Conduct disorder, antisocial personality disorder and psychopathy and violence 85
5.6.9 Aggressive attitudes 87
5.6.10 Instrumental violence 90
5.7 DISCUSSION 90
5.7.1 Validity of the Gunn Robertson Violence Scale as a measure of lifetime propensity to violence 90
5.7.2 Conduct disorder, antisocial personality disorder, psychopathy and violence 92
5.7.3 Aggressive attitudes 93
5.7.4 Instrumental violence 94
5.8 STRENGTHS AND LIMITATIONS 94
5.8.1 Strengths 94
5.8.2 Limitations 94

5.9 Conclusions 95

CHAPTER 6 CHILDHOOD ADVERSITY AND CONDUCT DISORDER 96

6.1 Introduction to published paper 96

6.2 Conduct disorder as a mediator of the association between cumulative childhood adversities and violence 103

6.3 Conclusions 103

CHAPTER 7 CONDUCT DISORDER, SUBSTANCE MISUSE AND PROPENSITY TO VIOLENCE IN SCHIZOPHRENIA 105

7.1 Abstract 105

7.2 Background 105

7.3 Hypotheses 106

7.4 Specific methodology 107

7.5 Results 107

7.5.1 Sample characteristics 107

7.5.2 Associations with violence 107

7.5.3 Substance use disorders and conduct disorder 108

7.5.4 Substance misuse, conduct disorder and violence 111

7.6 Discussion 112

7.6.1 Substance use disorders and conduct disorder 112

7.6.2 Substance use disorders, conduct disorder and violence 113

7.6.3 Early risk factors for violence 114

7.7 Strengths and limitations 115

7.7.1 Strengths 115

7.7.2 Limitations 115

7.8 Conclusions 116

CHAPTER 8 STRUCTURAL BRAIN ABNORMALITIES AND VIOLENCE IN SCHIZOPHRENIA 117

8.1 Abstract 117

8.2 Background 117

8.2.1 Structural imaging studies in schizophrenia 117
8.2.2 Structural imaging studies in schizophrenia and violence 119
8.3 HYPOTHESES 120
8.4 SPECIFIC METHODOLOGY 121
8.4.1 Data acquisition 121
8.4.2 Data processing 121
8.4.3 Statistical analyses 122
8.5 RESULTS 123
8.5.1 Demographics 123
8.5.2 Differences between patients and controls 125
8.5.1 Grey matter volume and violence in the patient group 129
8.5.2 Psychopathy 132
8.6 DISCUSSION 133
8.6.1 Schizophrenia 133
8.6.2 Violence and schizophrenia 135
8.6.3 Psychopathy 137
8.6.4 Caudate and violence in schizophrenia 138
8.7 STRENGTHS AND LIMITATIONS 140
8.7.1 Strengths 140
8.7.2 Limitations 141
8.8 CONCLUSIONS 141
CHAPTER 9 DISCUSSION 142
9.1 ABSTRACT 142
9.2 BACKGROUND 142
9.3 NOVELTY OF STUDY 142
9.3.1 Pre-morbid conduct disorder 142
9.3.2 Quantification of violence 143
9.4 LIMITATIONS 143
9.5 SUMMARY OF FINDINGS 144

9.5.1 Violence, aggressive attitudes and conduct disorder 144
9.5.2 Childhood adversity 144
9.5.3 Substance use disorders 145
9.5.4 Structural imaging 145
9.6 Discussion of findings 146
9.7 Hypothetical pathway to violence in schizophrenia 148
9.7.1 Positive psychotic symptoms 149
9.7.2 Genetics 150
9.7.3 Imaging 151
9.8 Contributions to knowledge 151
9.9 Clinical implications 152
9.9.1 Assessment 152
9.9.2 Intervention 153
9.10 Future directions for research 154
REFERENCES 156
APPENDIX A. ETHICAL APPROVAL 175
APPENDIX B. ALCOHOL AND DRUGS QUESTIONNAIRE 182

Table of Figures

Figure 1-1 Schneider's first rank symptoms of schizophrenia 17

Figure 5-1 Gunn Robertson Violence Scale (GRVS) ratings in patients and controls 83

Figure 7-1 Frequency of alcohol use before 15 years old in participants with schizophrenia (n=54) 109

Figure 7-2 Frequency of alcohol use between 15 and 18 years old in participants with schizophrenia (n=54) 109

Figure 7-3 Frequency of cannabis use before 15 years old in participants with schizophrenia (n=54) 110

Figure 7-4 Frequency of cannabis use between 15 and 18 years old in participants with schizophrenia (n=54) 110

Figure 8-1 Brain regions with reduced grey matter volume in patients compared to controls (uncorrected at threshold of p<0.001) 126

Figure 8-2 Brain regions with reduced grey matter volume in patients compared to controls that survived FWE correction 127

Figure 8-3 Brain regions with greater grey matter volume in patients compared to controls (uncorrected at threshold of p<0.001) 129

Figure 8-4 Scatter plot of grey matter volume of the cluster in left caudate (-2 12 4) and GRVS score with line of best fit and 95% confidence intervals 130

Figure 8-5 Brain regions in which GRVS score predicted greater grey matter volume (uncorrected at threshold of p<0.001) 131

Figure 8-6 Regions in which GRVS score predicted greater grey matter volume (uncorrected at threshold of p<0.001) 131

Figure 9-1 Associations between variables under investigation 147

Figure 9-2 Hypothetical pathway to violence in schizophrenia 149

Table of Tables

Table 2-1 Genetic studies of association between schizophrenia and violence 37

Table 2-2 Structural magnetic resonance imaging studies of schizophrenia and violence 39

Table 2-3 Functional magnetic resonance imaging studies of schizophrenia and violence 42

Table 3-1 Reliability and validity of violence measurement tools 55

Table 4-1 Timeline showing process attempting to obtain permission to Police National Computer records for participants 67

Table 5-1 Correlations with propensity to violence among patients (n=54) 77

Table 5-2 Group differences for key clinical characteristics 78

Table 7-1 Comparison of frequency of alcohol and cannabis use in those with and without pre-morbid conduct disorder 108

Table 7-2 Lifetime history of substance use disorders and pre-morbid conduct disorder 111

Table 8-1 Demographic characteristics of scanned participants 123

Table 8-2 Clinical demographics of scanned patients (n=23) 124

Table 8-3 Comparison of brain volumes of patients and controls 125

Table 8-4 Brain regions where patients had reduced grey matter volume compared to controls (uncorrected at threshold of $p<0.001$) 126

Table 8-5 Brain regions where patients had greater grey matter volume compared to controls (uncorrected at threshold of $p<0.001$) 128

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Statement of contribution

The research that forms this thesis has been undertaken as part of a joint project to investigate the clinical and neurocognitive factors associated with violent behaviour in men with schizophrenia. Broadly, my research concerns the clinical factors, and the research of my collaborator, Dr Stephanie Harris, focused on neurocognitive factors and is published in her thesis entitled Identifying Neurocognitive Factors Associated with Violence in Schizophrenia (Harris, 2014).

We jointly designed the study; this included deciding on the focus of the research, agreeing the general methodology and selecting the sample to be studied. I determined the hypotheses to be investigated in this thesis and how this would be achieved. Together we developed the protocol and made the application for ethical approval. We both recruited and consented participants for the study, arranged the MRI scans and accompanied the participants to the scans.

I selected and performed all the clinical assessments and collected and collated the information about a history of violence. Dr Harris conducted the neurocognitive assessments; the only data determined from her assessments that I have used in my analyses is Intelligence Quotient (IQ). All other data included in this thesis I collected and assessed myself.

Dr Harris and I undertook a literature review as joint first authors, which is included in chapter 3 of this thesis. In chapter 8, I undertook the statistical analyses in SPSS and Dr Marco Picchioni (PhD supervisor) undertook the imaging analyses in SPM. All other aspects of the literature reviews and analyses are my individual work.

As chapters 3 and 6 are published papers and are included in their final published form in accordance with thesis guidelines, the references do not appear in the main reference list of the thesis.

Abbreviations

Abbreviations are described in full at the point of first usage in the thesis; those used most commonly are also listed here:

ASPD	antisocial personality disorder
BPAQ	Buss Perry Aggression Questionnaire
CD	conduct disorder
CECA-Q	Childhood Experiences of Care and Abuse Questionnaire
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
GRVS	Gunn Robertson Violence Scale
MCVI	MacArthur Community Violence Instrument
PANSS	Positive and Negative Syndrome Scale
PCL:SV	Psychopathy Checklist Screening Version
SUD	substance use disorders

Chapter 1 Introduction to Schizophrenia

1.1 Abstract

In this chapter the diagnostic features of schizophrenia and its epidemiology and aetiology are described. The clinical management of the illness is also outlined.

1.2 Background

Schizophrenia is a psychiatric disorder that falls within the category of psychotic illnesses. It is characterized by the presence of certain symptoms and signs, in particular delusions, disorganization of thinking and hallucinations. The illness can be differentiated from other psychotic illnesses, such as psychotic depression and delusional disorder, by careful consideration of the diagnostic criteria (see 1.3.5). The presence of hallucinations and delusions, in the absence of prominent mood symptoms or organic cause, is often conceptualized as the core of schizophrenia. Due to the pervasiveness of the deficits associated with schizophrenia and its often chronic course, it is among the top ten leading causes of disease-related disability in the world (Tandon et al., 2008b).

The term schizophrenia was derived from the early observation that the illness is typified by a splitting of the mind (Bleuler, 1911), from the Greek words ‘schizo’ (split) and ‘phren’ (mind). The fundamental symptoms of schizophrenia proposed by Bleuler, referred to as Bleuler’s four As, were Ambivalence, Autism, Affective incongruity and loosening of Associations. His view of schizophrenia had a significant impact on clinical practice, particularly in the United States of America. In Europe, the work of Schneider was influential; he described first rank symptoms (see figure 1-1), arguing that the presence of one of these symptoms, in the absence of organic disease, was positive evidence for schizophrenia (Oyebode, 2008). Indeed the presence of first rank symptoms alone (without considering other diagnostic criteria) correctly identifies people with schizophrenia 75% to 95% of the time (Soares-Weiser et al., 2015).

Auditory hallucinations in the following form:

- Two or more voices discussing the patient or arguing about them
- Voices commenting on their thoughts or behaviour
- Audible thoughts

Passivity experiences

- Somatic passivity (external influence on the body)
- Passivity of affect (‘made’ feelings)
- Passivity of impulse (‘made’ drives)
- Passivity of volition (‘made’ volitional acts)

Passivity of thought

- Thought withdrawal
- Thought insertion
- Thought broadcast

Delusional perception (a normal perception which the patient falsely believes has special meaning for them)

Figure 1-1 Schneider's first rank symptoms of schizophrenia (adapted from Oyebode, 2008)

1.3 Diagnosis

1.3.1 Positive symptoms

Positive psychotic symptoms are principally thought disorder, delusions and hallucinations. Disorders in the form of thinking relate to abnormalities in the associations between thoughts and are a key diagnostic feature of schizophrenia. Features of formal thought disorder include: derailment (one thought slides onto another); substitution (a major thought is substituted by a subsidiary one); omission (omission of a thought or part of it); fusion (different elements of thought are interwoven) but can be difficult to distinguish from one another clinically (Casey and Kelly, 2007).

Delusions are a '*false, unshakeable belief that is out of keeping with the patient's social and cultural background'* (Casey and Kelly, 2007). Although this traditional definition of a delusion includes that the belief is false, this does not necessarily have to be the case. For example, a patient may have delusions of jealousy, yet it could be true that their partner is having an affair; it is the abnormal thinking that has led to the belief and the fact that it is not amenable to reason that make it a delusional belief. Delusions are judgements that are held with extraordinary conviction and subjective certainty and are impervious to compelling counterargument (Oyebode, 2008). Amongst the most common types of delusion in schizophrenia are delusions of persecution, delusions of reference, grandiose delusions, religious delusions and delusions of control. Delusions can also occur in severe affective illnesses (when the delusions will often be mood congruent, for example grandiose delusions in mania), or in delusional disorder (when the delusions would not be bizarre and no other symptoms of schizophrenia are present).

Hallucinations are '*a false perception which is not a sensory distortion or misinterpretation, but which occurs at the same time as real perceptions'* (Casey and Kelly, 2007). For the person experiencing an hallucination, they are a normal sensory experience, but one quality of a normal object perception is likely to be absent – 'publicness', often the person hallucinating does not believe that others can share their experience (and may give a delusional explanation for this) (Oyebode, 2008). Hallucinations can occur in any of the five senses and also with somatic sensation. Certain types of auditory hallucinations are of particular diagnostic significance for schizophrenia (see figure 1-1). Hallucinations may be intimately linked to delusional beliefs, for example a patient with the gustatory hallucination of a metallic taste to their food may have a delusional explanation of being poisoned.

1.3.2 Negative symptoms

Negative symptoms represent a withdrawal or lack of function and include emotional apathy, slowness of thought and movement, lack of motivation, poverty of speech and social withdrawal. Negative symptoms are harder to recognise than positive symptoms and can be mistaken for depression and other conditions. The presence of negative symptoms can be a

considerable barrier to rehabilitation. Prognosis, and the patient's and their carers' quality of life, is probably affected to a greater extent by negative, rather than positive, symptoms (Oyebode, 2008).

1.3.3 Cognitive deficits

Whilst not forming part of current diagnostic criteria, cognitive deficits in schizophrenia have been extensively documented. These deficits are present prior to the first episode of psychosis and particularly include memory, attention and executive functioning impairments, and may be related to poor prognosis (Gopal and Variend, 2005). Some patients may report changes in their memory but often cognitive deficits are only detected when specific tests are performed. Memory deficits are associated with greater severity and chronicity of illness, with the presence of negative symptoms and with formal thought disorder (Oyebode, 2008).

1.3.4 Clinical subtypes

Schizophrenia has been classified on the basis of symptoms into different subtypes, including paranoid schizophrenia, hebephrenic (or disorganized) schizophrenia and catatonic schizophrenia. Paranoid schizophrenia is characterized by delusions and hallucinations, as described in 1.3.1 and 1.3.2. In hebephrenic schizophrenia there is disorganized speech and behaviour and inappropriate affect. The psychomotor disturbance of catatonic schizophrenia includes symptoms such as posturing and mutism. Paranoid schizophrenia is the most common subtype (Sartorius et al., 1974) and is the focus of this thesis. These subtypes are no longer used in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM), (see 1.3.5.2), one of the two major classification manuals.

1.3.5 Operationalized diagnosis

1.3.5.1 ICD-10

In clinical practice in the United Kingdom, and much of Europe, the World Health Organization's International Classification of Diseases and Related Health Problems 10th revision (ICD-10), is utilized to structure the diagnosis of schizophrenia (World Health Organization, 1992). The diagnostic criteria for paranoid schizophrenia in ICD-10 require the

presence of persistent delusions, or thought echo, insertion, withdrawal or broadcast, or hallucinatory voices giving a running commentary on their behaviour, or discussing them between themselves for a month; or at least two of: persistent hallucinations, incoherent speech, catatonia or negative symptoms (World Health Organization, 1992).

1.3.5.2 DSM-IV and DSM-5

The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) is the operationalized criteria used in United States of America and many research studies worldwide. At the time of commencing the study described in this thesis, the fourth edition, DSM-IV (American Psychiatric Association, 2000) was current and are the diagnostic criteria utilized in this research. This has recently been updated to DSM-5 (American Psychiatric Association, 2013). The diagnostic criteria for paranoid schizophrenia in DSM-IV include the presence for one month of one of: bizarre delusions or running commentary or two voices arguing; or two of: other delusions, hallucinations, disorganized speech, catatonic behaviour, negative symptoms; and deterioration in functioning over at least six months(American Psychiatric Association, 2000). They also require that other medical, mood, psychotic and substance use disorders are ruled out.

DSM-5 raises the symptom threshold for a diagnosis of schizophrenia, requiring that an individual exhibit at least two of the specified symptoms (when previously one symptom of certain delusions or hallucinations was possible in DSM-IV). The other diagnostic criteria for schizophrenia in DSM-5 are largely similar to DSM-IV. However, DSM-5 diagnostic criteria no longer identify subtypes, as they were considered not to be helpful clinically due to patients' changing and overlapping symptoms, which decreased their validity.

1.4 Epidemiology

Transient, mild psychotic experiences can occur in healthy people (incidence of 2%) and are not associated with the functional impairment that would constitute illness (Hanssen et al., 2005). This has led to the conclusion that schizophrenia reflects a quantitative rather than qualitative deviation from normality, rather like hypertension or diabetes (Picchioni and Murray, 2007).

Schizophrenia typically presents in late adolescence or early adulthood. It is more common in men than women, with a male:female relative risk of approximately 1.4 (Tandon et al., 2008a). The age of onset is earlier in males and male gender is also associated with a poorer prognosis (Tandon et al., 2009).

Schizophrenia has a lifetime risk of around 1% (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The annual incidence of schizophrenia averages 15 per 100,000 and the point prevalence is 4.5 per population of 1000 (Tandon et al., 2008a). The prevalence is relatively high with respect to the incidence due to the onset in early adult life and the potential chronicity of the disorder.

1.5 Aetiology

1.5.1 Genetics

1.5.1.1 History

It has been recognised for many years that schizophrenia runs in families and now family and twin studies have demonstrated a strong genetic component (Lichtenstein et al., 2009, Sullivan et al., 2003), with heritability of between 64% and 81% respectively. Owing to this high heritability, there were many efforts to discover the causative genetic factors, and prior to the technological advances that heralded the genome-wide association study (GWAS) era, candidate gene studies were the focus. This strategy investigated candidate genes such as catechol-O-methyltransferase (COMT) and brain-derived neurotrophic factor (BDNF) but initially promising results were not consistently replicated. Current genomic evidence is inconsistent with an association with a particular gene and the effects originally reported in candidate gene studies are now considered very unlikely to be true (Farrell et al., 2015). However, it has recently been described that '*after two decades of frustration, genetic studies of schizophrenia have entered an era of spectacular success'* (Kavanagh et al., 2015). Technological advances have enabled analyses of genetic variation on a genome-wide scale, both for common alleles through genome-wide association studies (GWAS), as well as rare mutations through copy number variant analyses.

1.5.1.2 Common genetic variation

Schizophrenia is highly polygenic, with the suggestion that one third of the genetic liability could be explained by more than a thousand individual susceptibility single-nucleotide polymorphisms (SNPs) (Purcell et al., 2009). Over the years that followed, more loci with SNPs were reported at genome-wide significance (Hamshere et al., 2014). The largest GWAS in schizophrenia to date, identified 108 significant genetic loci, with associations particularly found among genes expressed in the brain (particularly relating to abnormal glutamatergic synaptic and calcium channel function), providing biological plausibility for the findings (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). That study suggested that schizophrenia is associated with many common genetic variants each of small effect size. GWAS studies have also found substantial overlap between schizophrenia, bipolar disorder and major depressive disorder, and a reduced, but still significant, overlap between schizophrenia and autistic spectrum disorder (Kavanagh et al., 2015). The genetic overlap of schizophrenia with mood disorders is consistent with the clinical syndromes having some common symptoms, while the overlap with autism provides genetic support for schizophrenia being a neurodevelopmental disorder (Murray and Lewis, 1988). It has been suggested that schizophrenia has a stronger neurodevelopmental component than bipolar disorder and lies on a gradient of decreasing neurodevelopmental impairment, between syndromes such as intellectual disability and autism on one hand, and bipolar disorder on the other (Craddock and Owen, 2010).

1.5.1.3 Rare genetic variation

Copy number variants (CNVs) are structural changes in chromosomes that result in deletions, duplications, inversions or translocations of large DNA segments. Unbalanced CNVs involve either deletion or duplication of segments of DNA, accordingly reducing or increasing the usual number of copies of the segment (Kirov et al., 2015). The earliest report of a rare genetic variation known to increase risk for schizophrenia, was a deletion CNV on chromosome 22q11, which causes velo-cardio-facial syndrome, a severe genetic disorder characterised by a reduced IQ and a number of physical anomalies and associated with a 30% risk of psychosis (Murphy et al., 1999). As new technology has permitted genome-wide CNV scans, so evidence has accrued for a wider role for CNVs in schizophrenia. Eleven confirmed CNV

loci have now been identified as rare but important risk factors in schizophrenia (Rees et al., 2014). It is estimated that about 2.5% of patients with schizophrenia (and 1% of controls) carry a large, detectable CNV at one of these loci (Rees et al., 2014). All CNVs for schizophrenia are also implicated in neurodevelopmental disorders (including autism and intellectual disability) and so are not specific to schizophrenia. Penetrance (the chance that CNV carriers will develop the disorder) is modest for schizophrenia CNVs but much higher for the CNVs for neurodevelopmental disorders (Kirov et al., 2015).

1.5.1.4 Summary

Over 100 specific common risk loci (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and at least 11 rare risk alleles (Rees et al., 2014) associated with schizophrenia have been identified. Common genetic variation is thought to account for far more of the variance in liability to schizophrenia than rare copy number variation (Farrell et al., 2015). There is evidence for shared genetic risk between schizophrenia, mood disorders and neurodevelopmental disorders and there is some evidence to suggest they are part of a spectrum (Kavanagh et al., 2015).

1.5.2 Environment

1.5.2.1 Environmental factors

There is consistent evidence from twin and family studies for common or shared environmental influences on liability to schizophrenia (Lichtenstein et al., 2009, Sullivan et al., 2003), with estimates between 4.5% and 11% respectively. A range of prenatal infections and obstetric complications (in particular premature birth and low birth weight) have been identified as risk factors for schizophrenia (Leask, 2004) and could act to subtly deviate early brain development. Childhood adversity has been shown to confer substantial risk for psychotic disorder (Varese et al., 2012, Morgan et al., 2014).

Associations are also seen with urban life, migration and cannabis. The association between urban areas and risk of schizophrenia is well established, with the incidence of schizophrenia increasing in a linear relationship with urbanicity as measured in terms of population size or density (Vassos et al., 2012). There is also consistent and strong evidence that the incidence

of all psychoses is higher in many migrant and ethnic minority populations in a number of countries (Morgan et al., 2010) but the exact reasons for this remain unclear. Early cannabis use, predating psychotic symptoms, has been shown to increase the future risk of schizophrenia (Arseneault et al., 2002), with meta-analyses reporting a doubling of the risk (Arseneault et al., 2004, Henquet et al., 2005). Indeed cannabis use and child abuse may combine synergistically to increase the odds of psychotic experiences (Morgan et al., 2014). For these environmental factors, pooled effect sizes from meta-analyses in the range of a two- to four-fold increase in risk, evidence of a dose-response relationship and population attributable risk fractions of 20%-35% have been reported which support the validity of the associations but a number of methodological uncertainties remain in validating environmental exposures (Van Os et al., 2014). The challenges to confirming the associations between environmental factors and schizophrenia include potential systematic information bias, confounding by genetic and other factors, and possible reverse causality. Integrated, large-scale longitudinal studies are required to overcome these factors and elucidate the specific role of environmental exposures in the aetiology of schizophrenia.

1.5.2.2 Gene-environment interactions

The gene-environment interactions (G X E) approach posits that the expression of an individual's genotype depends on environmental exposure and, vice versa, the effect of environmental exposure on risk depends on an individual's genotype. As described above, both genetic and environmental factors have long been considered important in the aetiology of schizophrenia. There is considerable variation in phenotype, as not all individuals exposed to environmental risk or carrying genetic risk variants develop the disorder, so G X E appears to be particularly relevant to schizophrenia (Van Os et al., 2014).

There have been a limited number of G X E studies in schizophrenia to date, the majority of which examine the interaction between cannabis or stress and COMT (Modinos et al., 2013). Research into gene by cannabis interactions is based on the hypothesis that genetic liability to psychosis may be expressed as differential sensitivity to the psychotomimetic effects of cannabis (Kahn et al., 2011). The first study to examine this issue (Caspi et al., 2005), utilized a longitudinal cohort design and found that regular use of cannabis in adolescence was

associated with an increased risk of developing a schizophreniform disorder in adulthood among carriers of the COMT Val allele. Similarly, a further study showed that carriers of the COMT Val allele, but not those with the Met/Met genotype, experienced increased hallucinations after using cannabis (Henquet et al., 2009). However, the findings of Caspi et al. (2005), were not supported by an analysis of nearly 500 cases which found no interaction between COMT Val158Met and cannabis use (Zammit et al., 2007). Evidence suggests that people with certain genetic polymorphisms are more sensitive to stress, and stress is a trait which is associated with the development of psychosis; hence a small number of studies have explored candidate gene and stress interactions in psychosis (Modinos et al., 2013). One study suggested that the COMT Val158Met polymorphism moderates affective and psychotic responses to stress in individuals with psychosis (Van Winkel et al., 2008). This finding was later replicated, with evidence that Met/Met genotype patients showed significantly increased psychotic and affective reactivity to stress, compared to the Met/Val and Val/Val genotypes (Collip et al., 2011).

G X E is an area of development for future research in schizophrenia, with a European network of researchers studying gene-environment interactions involved in the development, severity and outcome of schizophrenia (Van Os et al., 2014).

1.6 Management

1.6.1 Pharmacological

Antipsychotics are the mainstay of both acute and maintenance treatment for schizophrenia. In first-episode schizophrenia, antipsychotics achieve symptom reduction of around 60% (Kahn et al., 2008). Antipsychotic medication also significantly reduces relapse rates at one year, with a number needed to treat to benefit (NNT) of three (Leucht et al., 2012). First generation antipsychotics (such as haloperidol) have a greater propensity to cause extra-pyramidal side effects and tardive dyskinesia; while second-generation antipsychotics (such as olanzapine) have a higher propensity for metabolic side effects. Patients and their carers should be involved in prescribing decisions as fully as possible. The choice of antipsychotic will often be determined by the differing side effect profiles, as the magnitude of differing

efficacies of the various antipsychotics is small (Taylor et al., 2012). Monitoring the therapeutic effect, and any side effects, of the chosen drug is crucial.

If the first antipsychotic prescribed is not effective, or not tolerated, then a different antipsychotic should be commenced. If poor compliance is an issue due to lack of insight, then a depot antipsychotic may be necessary. If trials of two different antipsychotics have not been effective at controlling symptoms, then clozapine should be offered (National Institute for Health and Care Excellence, 2015, Taylor et al., 2012). Clozapine is more effective than other antipsychotics in reducing symptoms of patients with treatment resistant schizophrenia and decreasing hospital admission (Wahlbeck et al., 1999, Stroup et al., 2016).

1.6.2 Psychological

A form of cognitive behavioural therapy (CBT) has been developed for psychosis and helps people to re-evaluate their perceptions, beliefs or reasoning relating to the target symptoms, with the aim of reducing distress and improving functioning. CBT for psychosis has a small therapeutic effect on the symptoms of schizophrenia (Jauhar et al., 2014) and results in a reduction in persistent positive symptoms (Pfammatter et al., 2006). However, CBT intervention had no effects on rates of remission and relapse, or number of days spent in hospital, and so should be reserved for those with distressing medication-unresponsive positive symptoms (Garety et al., 2008). However, it has been identified as a national quality standard that all adults with schizophrenia are offered CBT for psychosis (National Institute for Health and Care Excellence, 2015), not just those with treatment-resistant positive symptoms; which some have argued is contrary to the evidence base (Perera and Taylor, 2014).

Family therapy includes psychoeducation for the patient and family members. Psychoeducation has been shown to improve compliance and reduce relapses in patients with schizophrenia (Morin and Franck, 2017). The specific aims of family therapy include: identifying precipitating stresses and likely future stresses inside and outside the family, planning strategies for managing these stresses, and accepting the reality of the illness and the need for treatment. Family intervention can improve coping skills and relapse rates of adults with schizophrenia and should be offered to all families (National Institute for Health and

Care Excellence, 2015). However, evidence suggests that people with schizophrenia have poor access to the recommended psychological interventions (Berry and Haddock, 2008).

1.7 Summary

Schizophrenia is a severe and enduring mental illness which has a significant impact on the wellbeing of patients and their families. It is characterized by delusions, hallucinations and thought disorder, and cognitive deficits are common. Its aetiology is complex and multifactorial, with evidence of both genetic and environmental influences. Antipsychotics are the mainstay of treatment and CBT for psychosis may be a beneficial adjunct for those with persistent psychotic symptoms.

Chapter 2 Selective Review of the Literature Relating to Schizophrenia and Violence

2.1 Abstract

This chapter describes the current literature relating to the link between schizophrenia and violence. It focuses on the clinical and biological factors which have been proposed to explain this association, including psychotic symptoms and co-morbid substance misuse and preliminary evidence of biological mechanisms from genetics and imaging studies. The emerging importance of premorbid conduct disorder in a potential pathway to violence in schizophrenia is discussed. It is concluded that supporting evidence is mixed and specific drivers for the association between schizophrenia and violence remain unclear.

2.2 Background

Understanding the pathways to violence in people with schizophrenia is crucial for risk management and effective treatment, however these pathways remain unclear. This is a vital issue, as almost 20% of patients with schizophrenia in the community will behave violently in a six month period (Swanson et al., 2006). This violent behaviour has far reaching ramifications for the patient, their families and society. The emotional cost of violent behaviour is extremely high for both patients and relatives. This is often compounded by close family members being the victims of the violent incident, with family members being the victim in half of homicides committed by patients with schizophrenia compared to around a third in homicides committed by the general population (Meehan et al., 2006). A criminal justice pathway to psychiatric care is more common in first episode of psychosis if there has been violent behaviour and is associated with a longer duration of untreated psychosis (Bhui et al., 2015). These patients often need several years' of treatment in a secure hospital and intensive, long-term follow-up in the community, necessitating considerable financial resources. Whilst understanding the causes of violence in schizophrenia is crucial, it is also important to remember that people with severe mental illnesses are much more likely to be the victims of violent crime than the general population (Teplin et al., 2005, Khalifeh et al., 2015).

There are many definitions of violence, one that is used commonly in clinical practice is: '*actual, attempted, or threatened harm to a person or persons'* (Webster et al., 1997). The term aggression is often used interchangeably with violence in the literature, despite different operational definitions (Serper, 2011). Aggression can be defined as any behaviour directed toward another individual that is carried out with the intent to cause harm (Anderson and Bushman, 2002). In contrast to violence, however, an act can be termed as aggressive even if it is not behaviourally expressed or no physical harm is sustained (Serper, 2011). Violence is generally, therefore, regarded as a more extreme form of aggression. The definition of violence and its measurement is discussed further in chapter 3.

At the commencement of this research study, there were two recent systematic reviews and meta-analyses (Douglas et al., 2009, Large and Nielssen, 2011) which examined the association between schizophrenia and violence. These papers formed the starting point of this selective review of the literature and allowed identification of the broad areas of interest of psychotic symptoms, antisocial personality disorder, substance misuse and childhood adversity. These topic areas were explored in more detail by examination of the original papers included in the meta-analyses, database searches and cross-referencing with other papers. In addition, genetics and imaging were emerging areas of research into schizophrenia and violence, although the number of studies is quite limited; these literature searches are described in 2.7.1 and 2.8.1.

2.3 Psychotic symptoms

Epidemiological studies have provided good evidence of a modest but clinically and statistically significant association between schizophrenia and the risk of violence (Douglas et al., 2009, Walsh et al., 2002, Arseneault et al., 2000, Large and Nielssen, 2011, Fazel et al., 2014). These studies have identified between a four- to six-fold increased risk of violent behaviour in schizophrenia (Fazel et al., 2009). Psychotic symptoms were an initial focus of studies that wanted to explore the drivers of this increased risk of violence in schizophrenia.

2.3.1 Positive psychotic symptoms

Several studies have concluded that the presence of positive psychotic symptoms (hallucinations and delusions) are associated with an increased risk of violence (Hodgins et al., 2003, Krakowski et al., 1999, Swanson et al., 2006, Daffern et al., 2005, Keers et al., 2014). However, other studies did not find evidence to support this association (Dean et al., 2007, Harris et al., 2010).

The MacArthur study was a highly influential prospective investigation that followed more than 1100 patients discharged from hospital to the community for one year, assessing them every 10 weeks, and compared them with people living in the neighbourhoods they were discharged to (Steadman et al., 1998). The study found that, in the absence of symptoms of substance abuse, there was no significant difference between the prevalence of violence by patients and by the general population (Steadman et al., 1998). The investigators also specifically found no association between any type of delusions and violence (Appelbaum et al., 2000). However, a reanalysis of data from the MacArthur study, carefully considering temporal proximity, indicated a relationship between several delusions and violence (Ullrich et al., 2014) (see section 2.3.2 below).

Threat/control-override symptoms, principally delusions of persecution (threat) and passivity (control-override), were advanced as a cognitive model for violence in psychosis (Link and Stueve, 1994). Initially this theory was corroborated by other studies (Link et al., 1998, Swanson et al., 1996, Swanson et al., 1997), however evidence from later studies did not support this (Appelbaum et al., 2000, Haddock et al., 2013). However, threat, but not control-override symptoms, have emerged as being a significant factor in aggressive behaviour in patients with psychosis (Nederlof et al., 2011, Stompe et al., 2004). Control-override symptoms (passivity) can be seen as more or less typical of schizophrenia. However, it has been noted that the threat symptoms encompass paranoia more generally, hence are comparatively unspecific and may occur widely outside of a schizophrenic illness (Stompe et al., 2004).

When considering paranoia more widely, rather than persecutory delusions, one study found that an association between aggression and psychosis proneness (sub-clinical psychotic symptoms) in the general population was mediated by threat (Fanning et al., 2011). A systematic review of paranoia and aggression in psychosis identified fifteen studies, primarily cross-sectional in design, which showed mixed support for an association between paranoia and aggression in both inpatients and community settings (Darrell-Berry et al., 2016). However, the authors noted that more methodologically rigorous studies tended to show a positive association between the factors. These findings are not isolated to patients and are also reflected in the general population. Data have demonstrated that paranoid ideation on a psychosis-continuum in the general population (without a psychotic disorder) was associated with violence severity and frequency (Coid et al., 2016), illustrating that paranoia is not just relevant as a risk factor for violence in those with schizophrenia but also in the general population.

2.3.2 Anger

There is an emerging literature exploring emotional reactions to psychotic symptoms, particularly anger, as possible correlates of aggressive behaviour in schizophrenia. Command hallucinations to harm others are associated with violence (McNiel et al., 2000), although not all studies have supported this finding (Haddock et al., 2013), and it has been demonstrated that anger and impulsivity are important in predicting compliance with command hallucinations to do harm (Bucci et al., 2013). Distress caused by the delusion partly explains the relationship between persecutory delusions and aggression (van Dongen et al., 2012). However, another study did not find a link between distress caused by a delusion and harming others (Haddock et al., 2013). An early study suggested that violent patients, rather than a non-violent group, were more likely to report that their delusion made them angry (Cheung et al., 1997b). Delusional beliefs implying threat were associated with serious violence but were mediated by anger due to the delusion (Coid et al., 2013). A reanalysis of data from the MacArthur study, considering temporal proximity, indicated a relationship between several delusions and violence, and that angry affect due to the delusions was the key factor in this pathway (Ullrich et al., 2014). A systematic review of angry affect and violence in the context of a psychotic illness, found that all studies reported higher anger scores for individuals with

schizophrenia who acted violently compared with the non-violent group (Reagu et al., 2013). Although the anger reported in these studies was noted to be related to active symptoms of schizophrenia, other factors that may provoke anger and could be present in individuals without psychosis may have played a role. Therefore, there are indicators that anger in response to delusions may be important in whether these beliefs are associated with violent behaviour.

2.3.3 Treatment

If psychotic symptoms are associated with violence then a logical hypothesis is that treating these symptoms with antipsychotics will reduce the risk of violence. The important moderating effect of treatment was highlighted by a meta-analysis of violence in first episode psychosis, which demonstrated that homicides were perpetrated by 1 in 630 new first episode patients and were associated with a longer duration of untreated psychosis (Large and Nielssen, 2011). Furthermore, non-adherence with medication is associated with violence in psychosis (Witt et al., 2013). More specifically the absence of treatment in schizophrenia is associated with violence, mediated by the emergence of persecutory delusions (Keers et al., 2014). Interestingly, clozapine is an antipsychotic that is considered to have specific anti-aggression action in schizophrenia (Frogley et al., 2012).

2.4 Conduct disorder, antisocial personality disorder and psychopathy

2.4.1 Conduct disorder

Conduct disorder (CD) reflects a pattern of persistent antisocial behaviour prior to the age of 15, symptoms described in DSM-IV include: initiating physical fights; forcing someone into sexual activity; being physically cruel to animals; deliberately destroying others' property; fire-setting with the intention of causing serious damage (First et al., 1997). CD is over-represented in patients with schizophrenia (Hodgins et al., 2008, Kim-Cohen et al., 2003) and is associated with an increased risk of violent behaviour in schizophrenia (Arseneault et al., 2000, Hodgins et al., 2008, Swanson et al., 2008). Indeed each CD symptom present before the age of 15 is associated with an increased risk of violent behaviour in adulthood in those

with severe mental illness (Hodgins et al., 2008, Hodgins et al., 2005). It may be that the clinical and non-clinical variables associated with violence differ in patients with schizophrenia with and without CD (Hodgins, 2008, Swanson et al., 2008, Heads et al., 1997). Therefore the factors that increase the risk of violence in schizophrenia may differ between those with and without prior CD. This makes it particularly important to consider the presence or absence of CD in violent patients with schizophrenia in future research that seeks to understand the nature of the association between schizophrenia and violence.

2.4.2 Antisocial personality disorder

Fewer than half of those with CD prior to the age of 15 will go on to develop adult antisocial personality disorder (Blair et al., 2014). In DSM-IV, a diagnosis of antisocial personality disorder (ASPD) requires evidence of CD prior to the age of 15 (First et al., 1997). ASPD is characterized by features such as a reckless disregard for the safety of self and others, deceitfulness, irritability and aggressiveness and consistent irresponsibility. People with ASPD have an increased risk of violence (Yu et al., 2012), including among those who also have schizophrenia (Volavka, 2014, Bo et al., 2013).

2.4.3 Psychopathy

A minority of those with ASPD are characterized by deficient affective experience, typified by a lack of empathy and remorse, as well as persistent reactive and instrumental aggression, and meet diagnostic criteria for psychopathy (Gregory et al., 2012) as defined by the Psychopathy Checklist-Revised (Hare et al., 1990). Psychopathy is significantly associated with violence and makes a substantial impact on violence among the general population despite its low prevalence (Coid and Yang, 2011). So although it is an uncommon condition, individuals with psychopathy are responsible for a considerable proportion of violence in the population. It is recognized that in forensic psychiatric settings, between 20% and 30% of patients with schizophrenia have high psychopathy scores (Dolan and Fullam, 2009). A range of studies conclude that psychopathy is an important predictor of future violence in schizophrenia (McGregor et al., 2012, Tengström et al., 2004, Tengström et al., 2000, Abushua'leh and Abu-Akel, 2006). There is some evidence that patients with schizophrenia and high psychopathy

scores may have more clinical characteristics in common with other offenders with psychopathy rather than other offenders with schizophrenia (Laajasalo et al., 2011, Bo et al., 2011).

2.5 Substance misuse

Substance misuse is associated with violence both in the general population (Coid et al., 2006, Fazel et al., 2009) and in people with schizophrenia (Swanson et al., 2006, Fazel et al., 2009), though controversy remains about the extent of its role in mediating the risk of violence in schizophrenia. Some evidence shows that substance misuse is one of multiple factors that increase the risk of violent behaviour in patients with psychotic illnesses (Daffern et al., 2005, Harris et al., 2010, Stompe et al., 2004); while other data suggests that the increased risk of violence is primarily mediated by co-occurring substance misuse, with a much lesser role for other factors (Elbogen and Johnson, 2009, Fazel et al., 2009). Adding complexity to this debate, a reanalysis of data from one of these studies (Elbogen and Johnson, 2009) found that those with severe mental illness, irrespective of the presence of substance abuse, were significantly more likely to be violent than those with no mental illness (Van Dorn et al., 2012), a finding later confirmed specifically for schizophrenia (Short et al., 2013). In short, it is now generally accepted that there is an increased risk of violence in schizophrenia, independent of co-morbid substance misuse, though substance misuse further increases that risk.

2.5.1 Substance misuse and conduct disorder

However the link between substance misuse and violence in schizophrenia may involve a more complex interaction with CD. Substance misuse is itself not a diagnostic criterion for CD, though CD is associated with an increased risk of substance abuse (Blair et al., 2014) and an increased risk of starting to use all classes of substances before the age of 18 (Hopfer et al., 2013). It may be that substance misuse occurs more commonly in patients with schizophrenia who had pre-morbid CD (Hodgins et al., 2005). However, lower levels of substance use may be associated with violence in those with CD compared to those without CD (Swanson et al., 2008). Therefore there appear to be interactions between pre-morbid conduct disorder,

substance misuse, and risk of violence in schizophrenia that may represent a trajectory from early CD to violence in adulthood.

2.6 Childhood adversity

Childhood physical abuse has been shown to be associated with later violent behaviour in general population (Elbogen and Johnson, 2009), patient (Hoptman et al., 1999, Witt et al., 2013) and prisoner (Sarchiapone et al., 2009) samples. However, less is known about the influence of other forms of childhood trauma on the risk of violence in people with schizophrenia.

Childhood adversity, that can occur in a variety of forms, is strongly associated with an increased risk for psychosis and could have a significant aetiological role (Varese et al., 2012). For example, a prospective study in adolescents showed that childhood trauma was strongly predictive of new adolescent psychotic experiences and that stopping the trauma ceased the psychotic experiences (Kelleher et al., 2013). There is also evidence that childhood abuse and the number of later life events combine synergistically to increase the odds of psychotic experiences beyond the effects of each risk factor alone (Morgan et al., 2014). However, other forms of childhood adversity, such as parental loss or separation also contribute to later psychopathology (Morgan et al., 2007). Hence there is a wider focus on the effects of childhood adversities in psychosis, rather than exclusively childhood trauma (Varese et al., 2012).

2.6.1 Childhood adversity and conduct disorder

Childhood adversity, including neglect and physical and sexual abuse, increases the risk of CD (Afifi et al., 2011, Foley et al., 2004, Maniglio, 2015, Villodas et al., 2014); while as already seen, CD is over-represented in patients who later develop schizophrenia (Hodgins et al., 2008). Patients with schizophrenia are more likely to have been exposed to a variety of adverse childhood events including physical and sexual abuse; parental divorce, parental death; domestic violence; and foster care (Gibbon et al., 2009, Rosenberg et al., 2007,

Bennouna-Greene et al., 2011). In summary, there is emerging evidence that childhood adversity, perhaps acting at critical periods of childhood development, is associated with CD, psychosis, and the risk of violence.

2.7 Genetics

2.7.1 Search strategy

A database literature search and manual cross referencing was conducted or English language studies relating to genetic studies in violent patients with schizophrenia. The following databases were searched: Scopus, EMBASE (1980-present), OVID Medline (1948-present), PsychINFO (2002-present); using combinations of the following search terms: schizophrenia, psychosis, gene*, COMT, MAO-A, antisocial, aggressi*, violen*.

2.7.2 Monoamine oxidase

Monoamine oxidase (MAO-A) is a critical regulator of monoaminergic neurotransmitter signalling, including at dopaminergic synapses throughout the brain. Its role in aggression has been implicated in animal and human models (Cases *et al*, 1995; Brunner & Nelen,1993; Buckholtz & Meyer-Lindenberg, 2009). However the studies in schizophrenia and violence have had largely negative results (see table 2-1). Four studies, including a total of 901 subjects, found no association between violence (Nolan et al., 2000, Koen et al., 2004) or aggression (Strous et al., 2003, Zammit et al., 2004) and MAO-A. One study considered agitation in patients with schizophrenia (Nikolac Perkovic et al., 2016), and also found no link to MAO-A. There was only one study that found a positive association between aggression and MAO-A (Fresan et al., 2007).

2.7.3 Catechol-O-methyltransferase

Perhaps more promising is the link between the catechol-O-methyltransferase (COMT) gene, schizophrenia and violence. COMT is one of the enzymes responsible for the catabolism of dopamine and noradrenaline in the brain. The Val allele of the COMT gene is associated with high enzymatic activity, whereas the Met allele is associated with low enzymatic activity.

Therefore the Met allele is associated with increased levels of catecholamines in the prefrontal cortex, which are associated with aggression in schizophrenia (Nolan et al., 2004, Soyka, 2011). Ten of thirteen studies of the COMT gene and violence in schizophrenia have suggested a significant association (see Table 2-1). Indeed two meta-analyses concluded that the Met allele of the COMT gene confers a significantly increased risk for violent behaviour in men with schizophrenia (Bhakta et al., 2012, Singh et al., 2012).

Table 2-1 Genetic studies of association between schizophrenia and violence

Author	**Measure**	**Instrument**	**Genes**	**n (total)**	**Results**
Strous (1997)	aggression	records, history	COMT	37	positive
Lachman (1998)	violence	records, history	COMT	55	positive
Kotler (1999)	homicide	records, history	COMT	92	positive
Nolan (2000)	violence	records, history	TPH MAO-A	55	positive negative
Jones (2001)	aggression	OAS	COMT	180	positive
Strous (2003)	aggression	LHA	COMT MAO-A	94	positive negative
Han (2004)	aggression	OAS	COMT	168	positive
Koen (2004)	violence (including to self)	PANSS	COMT MAO-A	63	negative negative
Zammit (2004)	aggression	OAS	COMT MAO-A	326	negative negative
Han (2006)	aggression	OAS	COMT	132	positive
Fresan (2007)	aggression	OAS	DRD4 MAO-A	71	positive positive

Hong (2008)	homicide	records, history	COMT	193	positive
Kim (2008)	aggression	OAS	COMT	165	positive
Tosato (2011)	aggression	OAS	COMT	80	positive
Koh (2012)	homicide	records, history	COMT TPH	232	negative positive
Guan (2014)	aggression	OAS	BDNF	579	negative
Perkovic (2016)	agitation	OAS, PANSS, PCL	MAO-A	363	negative

COMT = catechol-O-methyltransferase; MAO-A = monoamine oxidase A variant; TPH = tryptophan hydroxylase 1; BDNF = brain-derived neurotrophic factor; DRD4 = dopamine receptor D4; OAS = Overt Aggression Scale; PANSS = Positive And Negative Syndrome Scale; PCL = Psychopathy Checklist; LHA = Life History of Aggression scale

2.8 Imaging

2.8.1 Search strategy

A database literature search and manual cross referencing was conducted or English language studies relating to imaging studies in violent patients with schizophrenia. The following databases were searched: Scopus, EMBASE (1980-present), OVID Medline (1948-present), PsychINFO (2002-present); using combinations of the following search terms: schizophrenia, psychosis, imaging, MRI, antisocial, aggressi*, violen*.

2.8.2 Structural imaging

The results of the structural magnetic resonance imaging studies of violence in schizophrenia are summarized in Table 2-2. Region of interest (ROI) studies examine only certain brain regions hypothesized to be associated with the dependent variable, whereas whole brain studies investigate volume differences across the entire brain. Five of the structural imaging

papers were ROI studies and the remainder adopted a whole brain approach. The majority of papers identified presented results from two cohorts of patients. There are also considerable methodological inconsistencies across the imaging studies of schizophrenia and violence, including the definitions of violence employed and the inclusion of patients with co-morbid ASPD and substance misuse.

Table 2-2 Structural magnetic resonance imaging studies of schizophrenia and violence

Author	**Sample**	**Measure of violence**	**Region**	**Findings associated with violence in schizophrenia**
Hoptman (2002)	14 SCZ	LHA & BDHI	Right inferior frontal white matter	Higher trace
Hoptman (2005)	49 SCZ or SCZA	OAS & PANSS	Orbitofrontal	Increased grey matter (left) and white matter (bilateral) volume
Barkataki (2006)	13 SCZ + V 15 SCZ - V 13 ASPD + V 15 C – V	GRVS	Hippocampus	Reduced volume
Hoptman (2006)	49 SCZ or SCZA	OAS & PANSS	Caudate	Increased volume
Narayan (2007)	12 SCZ + V 15 SCZ - V 14 ASPD + V 15 C - V	GRVS	Medial inferior frontal and lateral sensory motor cortex	Reduced cortical thickness
Puri (2008)	13 SCZ + V 13 SCZ - V	Serious violent offence	Cerebellum Supramarginal	Reduced grey matter volume

Kumari (2009a)	10 SCZ + V 14 SCZ - V 14 C - V	GRVS	Hippocampus Orbitofrontal	Reduced grey matter volume
Lui (2009)	68 SCZ (first episode) 68 C	PANSS	Right anterior cingulate and middle temporal gyri	Reduced grey matter volume
Schug (2010)	32 SCZ + V 33 SCZ - V 31 C + V 14 other illness + V 47 C - V	Homicide	Right middle frontal and left inferior frontal gyri	Later birth order associated with reduced grey matter volume
Yang (2010)	22 SCZ + V 19 SCZ - V 18 C + V 33 C - V	Homicide	Hippocampus Parahippocampal gyrus	Reduced grey matter volume
Kumari (2013)	13 SCZ + V 15 SCZ - V 13 ASPD + V 15 C - V	GRVS	Hippocampus Putamen	Reduced volume Increased volume
Schiffer (2013)	27 SCZ + CD 23 SCZ – CD 27 CD 25 C	LHA	Hypothalamus	Increased grey matter volume
Hoptman (2014)	33 SCZ or SCZA 31 C	LHA & BPAQ	Right frontal pole Medial and lateral orbitofrontal gyri and inferior frontal gyri Anterior cingulate	Reduced cortical thickness

ROI = region of interest study; SCZ = schizophrenia; SCZA = schizoaffective disorder; ASPD = antisocial personality disorder; CD = conduct disorder; V = violent; C = control; OAS = Overt Aggression Scale; BDHI = Buss Durkee Hostility Inventory; PANSS = Positive And Negative Syndrome Scale; GRVS = Gunn Robertson Violence Scale; LHA = Life History of Aggression scale

These results provide consistent evidence, from both ROI and whole brain studies, of reduced grey matter volume in the hippocampus in patients with schizophrenia who are violent compared to those who are not (Barkataki et al., 2006, Yang et al., 2010, Kumari et al., 2009a, Kumari et al., 2013). There is also evidence of grey matter abnormalities in the inferior frontal region (Hoptman and Antonius, 2011, Narayan et al., 2007, Schug et al., 2010, Hoptman et al., 2014). Some results are conflicting, for example one study found that increased grey matter in the orbitofrontal region was associated with aggression (Hoptman et al., 2005) but another found decreased grey matter in the same region was associated with violence (Kumari et al., 2009a). One region of interest study found an association between increased volume of the caudate and aggression (Hoptman et al., 2006) but this region has not been identified in whole brain studies. One of the most relevant confounding factors that may explain some of the variance in these studies is the effect of antipsychotic medication on brain volumes (Soyka, 2011). It is recognised that the neuroimaging literature in schizophrenia and violence is in a period of development, in part attributable to the heterogeneous nature of violence and its measurement (Hoptman and Antonius, 2011).

2.8.3 Functional imaging

The results of the functional magnetic resonance imaging studies are summarized in Table 2-3. In brief, they show reduced frontal lobe activity in response to a working memory task and reduced activity in the prefrontal cortex, thalamus and caudate during the condition requiring inhibition a response inhibition task. There is some evidence of differing findings in patients with co-morbidities such as ASPD and psychopathy. There is early but consistent evidence of reduced resting state functional connectivity between frontal and medial temporal lobes in regions associated with aggression.

Table 2-3 Functional magnetic resonance imaging studies of schizophrenia and violence

Author	**Sample**	**Measure of violence**	**Task**	**Region**	**Findings associated with violence in schizophrenia**
Kumari (2006)	13 SCZ + V 12 SCZ - V 10 ASPD + V 13 C - V	GRVS	Working memory	Frontal Right inferior parietal	Severe working memory impairment with reduced activation bilaterally in frontal lobe and right inferior parietal lobe
Joyal (2007)	12 SCZ 12 SCZ + ASPD + SUD 12 C - V	Homicide	Go/no-go	Prefrontal cortex	Reduced activity in go/no-go task in those with co-morbidity
Barkataki (2008)	12 SCZ + V 12 SCZ - V 14 ASPD + V 14 C - V	GRVS	Go/no-go	Thalamus Caudate	Reduced activity in go/no-go task
Kumari (2009b)	13 SCZ + V 13 SCZ - V 13 ASPD + V 14 C - V	GRVS	Threat of electric shock	Occipital Temporal	Altered activity modulation in occipital and temporal lobes and exaggerated thalamic-striatal activity in response to threat
Dolan (2009)	12 SCZ + V + low PCL-SV	Violent offence	Facial affect	Amygdala	Blunted response to fearful faces in

	12 SCZ + V + high PCL-SV				those with co-morbid psychopathy
Hoptman (2010)	25 SCZ or SCZA 21 C - V	LHA & BPAQ	Resting state	Amygdala / ventral prefrontal cortex	Reduced functional connectivity between regions related to aggression
Hoptman (2014)	33 SCZ or SCZA 31 C	LHA & BPAQ	Resting state	Right frontal pole Left medial and lateral orbitofrontal gyrus Anterior cingulate	Reduced functional connectivity between regions related to impulsivity/aggression

SCZ = schizophrenia; SCZA = schizoaffective disorder; ASPD = antisocial personality disorder; V = violent; C = control; OAS = Overt Aggression Scale; PANSS = Positive And Negative Syndrome Scale; GRVS = Gunn Robertson Violence Scale; LHA = Life History of Aggression scale; PCL-SV = Psychopathy Checklist Screening Version; BPAQ = Buss Perry Aggression Questionnaire

2.8.4 Implications

The studies summarized above represent the totality of the neuroimaging evidence relating to schizophrenia and violence. Six of the papers identified presented results from the same cohort of patients. There are a very small number of studies, with modest sample sizes, and so the current evidence in this area is limited. There are also considerable methodological inconsistencies across these imaging studies in the definitions of violence employed (e.g. convictions, self-report, type and severity of violence) and in the inclusion of patients with co-morbid antisocial personality disorder (ASPD) and substance misuse.

Despite the methodological challenges, there is emerging evidence that patients with schizophrenia who are violent are characterized by a number of biological markers, principally

centred on medial temporal and frontal lobe volume deficits. There is evidence of generally impaired neural activity with some very early evidence of disordered structural and functional connectivity. More detailed investigation of violence in patients with schizophrenia, with appropriate consideration of the relevant co-morbidities, including antisocial personality disorder and substance misuse is required to elucidate which deficits, if any, are specific to violence in schizophrenia.

2.9 Challenges of research into violence and schizophrenia

2.9.1 Violence definition

Many previous studies have considered violent offending in schizophrenia as a homogenous entity. The studies reviewed varied considerably in terms of the definition of violence employed. Most studies used either a dichotomous measure of the presence or absence of violence, or of severe and less severe violence (the threshold often being assault causing injury or similar). The methods of obtaining information included self-report, criminal records, medical records and informants, either alone or in combination. Means of assessment included PANSS, OAS and criminal convictions. The variations cause challenges in comparing the results of studies. There would be benefits of utilizing a scale measure of violence to produce richer data (see chapter 3 for a wider discussion).

2.9.2 Co-morbidities

Study samples have usually included patients with a range of other co-morbidities, that themselves are independently associated with violence risk within the same experimental groups, for example antisocial personality disorder and substance misuse. This methodological limitation makes it then difficult to distinguish factors relating to violence associated with these co-morbidities from those specific to schizophrenia. The picture is further complicated by the use in previous studies of the broad term of psychosis rather than schizophrenia. It has been suggested that one way of differentiating sub-groups of patients with schizophrenia with differing propensities to violence is the presence of co-morbid CD. Therefore, pre-morbid CD may be a significant co-morbidity to consider in future studies.

2.10 Typologies of violence in schizophrenia

The findings reviewed in this chapter, have led to the suggestion that violence among patients with schizophrenia may follow at least two distinct pathways, one associated with premorbid conditions, including CD, and another linked with the acute psychotic symptoms of schizophrenia (Volavka, 2014, Bo et al., 2011, Volavka and Citrome, 2011, Hodgins et al., 2014). One way of conceptualizing these two pathways, has been the early-start offender and the late-start offender, which is a typology that has previously been applied to all criminal offenders and more recently to those with schizophrenia. Early-start offenders have higher rates of substance use disorders and higher psychopathy scores in adulthood than late-start offenders (Tengstrom et al., 2001, Van Dongen et al., 2014). It is suggested that late-start offending is primarily driven by positive psychotic symptoms rather than antisocial traits (Van Dongen et al., 2015).

Therefore, in an attempt to differentiate between patterns of violent behavior in schizophrenia, it has been proposed that future studies should distinguish between patients with schizophrenia with and without prior conduct disorder (Hodgins, 2008, Tengstrom et al., 2001). Hypothetically, these groups may differ both in key neurodevelopmental and more proximal risk factors, such as psychotic symptoms and drug misuse, which act to influence the risk of violence, with implications for the nature of that risk, its assessment, management and treatment.

2.11 Summary

There is a modest but statistically significant association between schizophrenia and violence. However, this link has massive clinical, societal and personal implications and contributes to increased stigma around mental illness. The specific drivers and their relative contributions to this association remain unclear. CD is over-represented in patients with schizophrenia and is associated with an increased risk of adult violent behaviour. Those with CD are more likely to experience childhood abuse and substance misuse, both of which are also associated with an increased risk of violence. Therefore, the relationships in early life between CD, childhood adversity and substance misuse may be of particular importance in understanding the pathway to violence in people with schizophrenia. Once the psychotic symptoms of the illness

are manifest, the evidence is mixed regarding whether hallucinations and delusions are linked to violence. However, there is emerging evidence that angry affect in response to delusions may mediate the association between delusions relating to threat and violent behaviour.

The genetic and neuroimaging literature on violence in schizophrenia is in a period of development. However, there is evidence that the Met allele of the COMT gene confers a significantly increased risk for violent behaviour in men with schizophrenia. In relation to imaging, there is almost entirely consistent evidence of reduced grey matter volume in the hippocampus in patients with schizophrenia who are violent. There is further evidence of probable grey matter volume loss and early evidence of impaired structural and functional connectivity between frontal and medial temporal lobes.

Chapter 3 Quantifying violence in mental health research

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3.1 Introduction to published paper

This paper describes a systematic review to identify and evaluate tools to assess violent behaviour. It was conducted as a means of identifying the best method of measuring and quantifying violence to utilise in this research study. As described in 2.9.1, many previous studies have considered violent offending in schizophrenia as a homogenous entity. It was considered important for this study, not to use a dichotomous presence or absence of violence to categorise participants, but to use a measure which allowed a richer data set relating to a range of violent behaviour. Therefore, the following paper aimed to assist in determining the best method of assessing violence for this study.

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Aggression and Violent Behavior

Quantifying violence in mental health research

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ABSTRACT

Research into mental illness and its relationship with violence has been constrained by inconsistencies in the definition and measurement of violent behavior. We conducted a systematic literature search of Scopus, EMBASE, PsycINFO, and Ovid Medline with search terms relating to the measurement, rating and quantification of violent behavior in mentally disordered populations. We identified nine tools designed to assess violence and critically evaluated them. Broadly, measurement tools tended to focus on multiple, but different, facets of violence, which included: severity of act, severity of outcome, frequency and intent, with each suggested as a valid outcome measure for violent acts. The use of multiple sources of information to inform assessment appears to provide detail; however, that detail is then often diluted as a result of dichotomization of sample groups. This presents methodological challenges for the field. Future studies should give consideration to the trade-off between preserving the richness of data and the difficulties associated with recruiting large patient samples. Studies should move from simply defining violence towards quantification across different dimensions of violence and using multiple sources of information.

Contents

1. Introduction . . . 696
1.1. Violence and mental illness . . . 696
1.2. General definition of violence . . . 696
1.3. Definitions of violence for research . . . 696
2. Method . . . 696
3. Results . . . 697
3.1. Assessments of violence identified . . . 697
3.1.1. Gunn Robertson scale . . . 697
3.1.2. Modified Overt Aggression Scale . . . 697
3.1.3. Violence Scale . . . 697
3.1.4. Lifetime History of Aggression . . . 697
3.1.5. MacArthur Community Violence Instrument . . . 697
3.1.6. Liverpool Violence Assessment . . . 698
3.1.7. Quantification of Violence Scale . . . 698
3.1.8. Crime and Violence Scale . . . 698
3.1.9. Attempted and Actual Assault Scale . . . 698
3.2. Methods used in previous research . . . 699
4. Discussion . . . 699
5. Conclusion . . . 699
Role of funding source . . . 700
Appendix A. Example of systematic search strategy — Scopus . . . 700
References . . . 700

Abbreviations: MOAS, Modified Overt Aggression Scale; LHA, Lifetime History of Aggression scale; QOVS, Quantification of Violence Scale; CVS, Crime and Violence Scale; Attacks, Attempted and Actual Assault Scale; VAS, Visual Analogue Scale.

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1. Introduction

In 1996, the World Health Organization declared violence to be a major global public health issue. Its effects span personal and societal health, economic output, and societal integrity; conservative estimates suggest that its annual total economic burden exceeds $40 billion (Butchart, Phinney, Check, & Villaveces, 2004). While global data are scarce, one estimate suggests that 1.6 million people died as a result of violence in 2000, 91% of them in low or middle income countries, with nearly one third dying through homicide (Krug, 2002). Many more are exposed to non-fatal violence, with interpersonal violence the biggest contributor (Krug, 2002). The exact scale of this non-fatal violence is unclear as data are incomplete. Therefore, the contributors and causes on a global scale are difficult to determine.

1.1. Violence and mental illness

A body of work has developed exploring the links between mental illness and interpersonal violence, recognizing that this relationship is both complex in terms of pathways and influences, but also bi-directional. Violence may influence psychopathology; for example, exposure to interpersonal violence in childhood and adulthood is consistently associated with an increased risk of depression, anxiety, and substance abuse (Cerda, DiGangi, Galea, & Koenen, 2012). Furthermore, people with severe mental illnesses are 11 times more likely to be the victims of violent crime than the general population (Teplin, McClelland, Abram, & Weiner, 2005).

From the opposite perspective, those with mental illnesses are also more likely to behave violently. There is good evidence to support an independent association between violence and schizophrenia (Fazel, Langstrom, Hjern, Grann, & Lichtenstein, 2009; Walsh, Buchanan, & Fahy, 2002); alcohol and drug dependence (Coid et al., 2006); and antisocial personality disorder (Yu, Geddes, & Fazel, 2012) and psychopathy (Coid & Yang, 2011). The link is perhaps most often considered for schizophrenia where almost 20% of patients living in the community with that illness will behave violently in a six-month period (Swanson et al., 2006). That violence can have far reaching ramifications for the patient, their carers, and society. The emotional cost of violence is extremely high for patients and their relatives, particularly as close family members are so often the victims in more than half of homicides committed by patients with schizophrenia (Meehan et al., 2006), compared to approximately one third in homicides committed by the general population. Following such an event, these patients are often treated for years in secure hospital settings and thereafter receive intensive, long-term follow-up in the community, with considerable personal liberty and societal implications.

Despite the personal and societal importance of violent behavior among patients with schizophrenia, remarkably little has been established about the nature of any illness-specific factors which may contribute to that association. Research in this area is generally impeded by significant heterogeneity in the definition, categorization, and quantification of violence. For example, a recent meta-analysis of psychosis and violence commented that one of the challenges of research in this area is that there is no accepted definition or measure of violence (Douglas, Guy, & Hart, 2009). The authors further pointed out that perhaps as a consequence of that failure, many studies did not define violence at all, and that the frequently employed practice of dichotomizing violence as present or not, may deliver an impoverished criterion variable (Douglas et al., 2009).

1.2. General definition of violence

Definitions of violence vary widely in their scope in the literature; however, one commonly accepted description from the World Health Organization is 'the intentional use of physical force or power, threatened or actual, against oneself, another person, or against a group or community, that either results in or has a high likelihood of resulting in injury, death, psychological harm, maldevelopment, or deprivation' (Krug, Mercy, Dahlberg, & Zwi, 2002). That definition encompasses all forms of violence, which are further divided into self-inflicted, interpersonal and collective (social, political or economic violence committed by groups of individuals) violence.

The term aggression is often used interchangeably with violence in the literature, despite different operational definitions (Serper, 2011). Aggression broadly speaking may be defined as "any behavior directed toward another individual that is carried out with the proximate intent to cause harm" (Anderson & Bushman, 2002). In that definition, the victim must also be motivated to avoid being harmed (act is not consensual). In contrast to violence, however, an act can be termed as aggressive even if it is not behaviorally expressed or no physical harm is sustained (Serper, 2011). Violence is generally, therefore, regarded as a more extreme form of aggression.

1.3. Definitions of violence for research

There are challenges and complexities in defining and quantifying violence for research purposes. There are four key factors which it can be argued influence the character of any violent incident: planning, intent, nature, and outcome or consequences (Tyrer et al., 2007). Differences in any or all of these factors can affect how one evaluates the behavior. For example, if somebody knowingly and willingly stabs another person, the physical and thus legal outcomes can be very different depending where on the body they stab them. These may vary not only by intent but also by chance, with the type of weapon used, or the availability of emergency medical intervention. It could be argued that for the assessment of many acts of violence it is in fact the intent when stabbing someone that may be equally or indeed more important. In addition, frequency or density of violent behavior across a person's lifetime may be another important index of violence propensity. It has been argued that a serious flaw of many measures of violence is their conflation of violence severity with injury outcome and that more objective, behavioral (Bowers, 1999) and perhaps cognitive components to assault severity are needed.

One attempt at such an approach features in structured professional judgment guides. In clinical practice, the HCR-20 is a widely used risk assessment guide. It offers a definition of violence as 'actual, attempted, or threatened harm to a person or persons; the resulting damage to a victim is not the defining feature of a violent act. Rather it is the act itself' (Webster, Douglas, Eaves, & Hart, 1997). Using that definition, the outcome or consequences of the behavior are not considered key; it is the behavior itself that warrants consideration as violent. While the HCR-20 does not incorporate intent as a part of its definition, it does include it as an element that clinicians must assess as part of the formulation component of undertaking this risk assessment.

While definitions of violence employed in the literature vary, using a threshold model to categorize an experimental sample of people into violent and non-violent groups does not allow for a rich and perhaps even accurate description and analysis of violent behavior. In order to advance our understanding of this complex inter-relationship, a method of quantifying violence is needed to provide more detailed information than its mere historical presence or absence. Therefore, we set out to review the literature relating to the measurement or quantification of violence, with the aim of identifying the available tools or assessments and assess their relative strengths for future research projects.

2. Method

We conducted a systematic literature search of manuscripts that comprised specific assessments of violence, using EMBASE, OVID Medline, PsycINFO, and Scopus databases in March, 2013 (example in Appendix A) and manual cross-referencing of the returned papers. Search terms used were "violence scale", "violence measure", "violence

tool", "violence assessment", "violence rating", "assessment of violence", "measurement of violence", and "quantification of violence". Of the returned abstracts, those in which a specific violence measurement instrument had been described or used were extracted. Studies examining violence risk assessment, violence in adolescent populations, child abuse, domestic violence, and collective violence were excluded. We identified a total of nine specific violence measurement instruments.

3. Results

3.1. Assessments of violence identified

3.1.1. Gunn Robertson scale

The Gunn Robertson scales have evolved to describe lifetime offending behavior in prisoners that included violent conduct as well as other offending behaviors such as theft and motoring offenses (Gunn & Robertson, 1976). Each type of offending is rated on its own five point sub-scale. The violence scale incorporates consideration of both the frequency and nature of the violence, the victim's health consequences, as well as the criminal justice outcome for the perpetrator (Gunn & Robertson, 1976): 0 = No convictions. Never gets into fights; 1 = No convictions. Evidence of minimal violence, i.e. occasional fights or damage to property; 2 = One or two convictions for violence, or repeated acts of violence to person or property, none of which has caused serious damage to life or health; 3 = Three or more convictions for violence; 4 = One or more severely violent episodes in which someone's life or health has been seriously damaged.

The Gunn–Robertson scale was later adapted to yield ratings of both severity and physical outcome of the index offense specifically (Wong, Lumsden, Fenton, & Fenwick, 1993). In a UK high secure hospital, the index offense was rated between 0 (completely non-violent offense) and 4 (victim died or health seriously endangered). This score for the index offense was then summed with the original Gunn–Robertson scale (lifetime violence score) to produce a total violence rating.

Kumari et al. (2009) compared violent and non-violent patients with schizophrenia, patients with antisocial personality disorder and healthy controls. They summed the original Gunn–Robertson scale to assess lifetime violence (0–4); and the amended scale for the index offense (0–4), however they dichotomized their sample, using a cut-off combined score of 5 for inclusion in the violent group. The authors suggest the cut-off of 5 on this scale equated to one 'fatal or near fatal act of violence against another and at least one other moderately serious incident of violence' (Kumari et al., 2009). The strength of the Gunn–Robertson scale is that, unlike other violence assessment tools, it incorporates data on both criminal justice interventions as well as self-reported violent incidents that remain undetected by the police or courts. However, despite that principle, some points on the scale remain exclusively defined by convictions, not incorporating self-report.

3.1.2. Modified Overt Aggression Scale

The original Overt Aggression Scale (Yudofski, Silver, Jackson, Endicott, & Williams, 1986) was modified by amending the item definitions, adding a zero point on the scale and introducing a weighting factor based on the nature of the violent act. The resulting Modified Overt Aggression Scale (MOAS) (Kay, Wolkenfeld, & Murrill, 1988) was designed to be a retrospective weekly rating on a five point scale of 0–4 of the severity of the most serious aggressive incident that the participant is involved in. The MOAS includes four aggression dimensions comprising: verbal aggression, physical aggression, property damage, and self harm. Scores are weighted according to the nature of the aggression, for example, with physical aggression receiving four times the weighting of verbal aggression. The physical aggression scale is as follows: 0 = none; 1 = makes menacing gestures, swings at people, grabs at clothing; 2 = strikes, pushes, scratches, pulls hair of others (without injury); 3 = attacks others, causing mild injury (bruises, sprains, welts, etc.); and 4 = attacks others causing serious injury (fracture, loss of teeth, deep cuts, loss of consciousness, etc.). These example behavior descriptors act as anchor-points to improve the ease and reliability of scoring.

A time sampling and reporting window of one week on the MOAS leads to weekly scores for violence, and that allows comparisons over time to determine changes in the frequency and severity of aggression and violence. The scale has good inter-rater reliability (between 0.85 and 0.94) (Bowers, 1999). It is also sensitive to low severity incidents; however, it merges the nature of the behavior, outcome and severity, which results in diverse behaviors being grouped together. Also the MOAS takes no account of antecedents, perpetrator intent, or legal consequences. The original Overt Aggression Scale and the updated MOAS are the most extensively utilized violence quantification scales in the literature and have featured in multiple and diverse studies of in-patient aggression (Arango, Barba, Gonzalez-Salvador, & Ordonez, 1999; Krakowski & Czobor, 2012; Nolan et al., 2005).

3.1.3. Violence Scale

This scale was designed to be completed by nurses (Morrison, 1993) to assess inpatient violence. Fifteen statements assess violence to others, violence to property, and violence to self, and are rated on a four point anchored frequency scale ranging from never to frequently. The Violence Scale is moderately internally consistent and considered to be a significant improvement over previous dichotomization techniques (Morrison, 1993). The scale is quick and simple to complete by psychiatric nurses, facilitating its routine use in busy inpatient settings. The scale has not been used frequently, but is often cited as a basis for other work (Bowers, 1999), and has influenced the development of other violence measures, for example, the Quantification of Violence Scale (Tyrer et al., 2007) and the Actual and Attempted Assault Scale (Bowers, Nijman, & Palmstierna, 2007) discussed below.

3.1.4. Lifetime History of Aggression

The Lifetime History of Aggression scale (LHA) (Coccaro, Berman, & Kavoussi, 1997) records the frequency of a variety of aggressive, violent, and antisocial behaviors across the lifetime. A total of 11 items (e.g., school disciplinary problems) are each rated on a five-point anchored frequency scale: 0 = never happened; 1 = only happened once; 2 = happened a couple or a few times (e.g. 2–3); 3 = happened several times (e.g.4–9); 4 = happened many times (e.g. 10+); and 5 = happened so many times that I couldn't give a number. The 11 items are divided into three subscales (aggression, consequences/antisocial behavior, self directed aggression). The authors proposed that the summed total score, ranging between 0 and 55, represents an estimate of the person's intrinsic aggressive tendencies with a higher score indicating a greater history of aggressive behavior.

The LHA in mentally disordered populations has high inter-rater and test–retest reliability and has been validated against the MOAS and Buss Durkee Hostility Inventory (Coccaro et al., 1997). It has been used in several studies in mentally disordered populations including neuro-imaging studies of schizophrenia and violence (Hoptman et al., 2002, 2010). Despite this, the LHA assesses only aggression, that is, less severe violence, with only one item relating to physical interpersonal violence. The scale reports on behavior across the lifespan, but does not consider planning, intent, or outcome of individual behaviors.

3.1.5. MacArthur Community Violence Instrument

The MacArthur study and its associated Instrument (Steadman et al., 1998) remain still perhaps the most influential metric for violence categorization. That study focused on recent community violence and

used different categories of aggressive behavior that included: throwing an object; pushing, grabbing or shoving; slapping; kicking; biting; choking; hitting or beating up; forcing sex; threats with a weapon; and use of a weapon. In the original study, incidents of violence/aggression were dichotomously categorized, either as manifesting "violence" (battery that resulted in physical injury, sexual assaults, use of a weapon, threats with a weapon in hand); or "other aggressive acts" (battery that did not result in injury). This framework has been repeated in multiple subsequent studies of violence and mental disorder for example (Hodgins, Alderton, Cree, Aboud, & Mak, 2007; Swanson et al., 2008). While the instrument was originally used to assess violence in the previous 10 weeks, it has subsequently been used to retrospectively assess lifetime violence using the same violence categories and other aggressive acts (McGregor, Castle, & Dolan, 2012).

Re-analysis of the MacArthur items broadly supports their validity for assessing violence (Michie & Cooke, 2006). In that study, 150 prisoners were asked about the nature and frequency of their violence. Using the original MacArthur severity-ordered scale and the frequencies reported, responses were re-coded into three categories: behavior never occurred, behavior occurred less than or equal to the median frequency, and occurred more than the median frequency. Exploratory and confirmatory factor analysis revealed a two factor solution achieving an excellent fit to the data: 'violence based on weapon use'; and 'violence without weapon use'. The data suggested two distinct forms of violence that in some respects mapped onto the earlier conceptual framework of the original MacArthur. This provides support for the violence versus any other aggressive acts distinction used in the MacArthur study; however, the later model suggested that the threshold might be higher, that is at the level of weapon use, rather than any violence, where for example the distinction may in part be driven by instrumental or reactive motives.

Michie and Cooke (2006) reported that clinical and vulnerability factors widely associated with violence were differentially related to the two factors in their model. Violence with weapon use was associated both with psychopathy and childhood history of violence, while violence without weapon use was linked to impulsivity and elevated trait levels of anger. The authors suggested an evidence-based ordered severity scale of the underlying traits that was, from lowest to highest:1) Hitting or beating up; 2) pushing, grabbing or shoving; 3) kicking, biting, choking; 4) threats with a weapon; 5) throwing an object; 6) using a weapon; and 7) any other violent acts. The authors noted that some of the items needed greater refinement in order to improve the scale's predictive accuracy and discriminative power. For example, item 3 contained conceptually disparate acts ranging from kicking, biting, and choking. Nevertheless, analysis revealed this to be a highly informative item. It was suggested that measurement accuracy may be increased by differentially assessing each behavior, and the addition of new items.

3.1.6. Liverpool Violence Assessment

This assessment was designed to measure patterns of severe violence using a semi-structured interview to obtain descriptions of violent behavior and associations with other factors (Nathan, Rollinson, Harvey, & Hill, 2003). Ratings made on the basis of the interview consider all violence within a five-year period while the person is outside institutions. Summary scores are made for severity of worst violence and frequency of violence (0–6), and overall violence (0–4), where 0 constitutes "no violence", and 4 "habitual and serious violence". In addition, "associated factors" such as alcohol and drugs, weapon use and planning are rated. The authors found significant correlations between violence scale score (severity, frequency, and overall) and official records (severity of index offense), but the frequency of self-reported violence was much higher than official records (Nathan et al., 2003). Despite the scales' strength of independently rating frequency and severity, to our knowledge this scale has not been used in subsequent studies of violence and mental disorder.

3.1.7. Quantification of Violence Scale

More recently, the Quantification of Violence Scale (QOVS) attempted to develop an index of the severity of violence. It included assessment of planning and intent, as well as the victim consequences (Tyrer et al., 2007). The scale was developed in the UK 'Dangerous and Severe Personality Disorder' (DSPD) services for men with psychopathy. Thus far, however, it has not been employed in studies in other mentally disordered populations. The scale includes 30 items designed to comprehensively capture a range of violent behaviors, incorporating both data on the location of the violent behavior and the nature of the relationship between perpetrator and victim.

The QOVS can be scored in one of two ways. In the numerical version, the planning, intent, and consequence scores are summed to deliver a total score. The authors proposed that the total score reflected a more precise index of severity; however the authors acknowledge that accurately scoring in this way, particularly on the intent/planning component, requires a high level of detailed interview information and is largely subjective/has the poorest inter-rater reliability. The hierarchical approach involves matching a violent behavior as closely as possible to a behavior on the 30-item scale and assigning to it the corresponding score. Without specific information about the location of the offense and the victim, this can be difficult to score. The relationship between the perpetrator and victim as well as location can also have a significant impact on violence severity rating. For example, throwing a heavy book at a child in some else's home is ranked as 16 (cut-off for severe violence), whereas throwing a can of beer at a stranger in the street is ranked as 6, and throwing a can of beer at a friend at home is ranked as 1 (lowest in severity). This could be a reflection of the social context when assessing the acceptability of certain types of behavior.

Both scoring versions had good inter and test–retest reliability, and good validity in clinical populations (Tyrer et al., 2007). Despite this, the QOVS was specifically designed for the assessment of severe violence but was validated against the Modified Overt Aggression Scale (MOAS) (Tyrer et al., 2007). As the MOAS also assesses low severity events, this resulted in a high proportion of events being scored on the MOAS, but not reaching the threshold to be scored on the QOVS, as this assesses only severe violence. In this study, only three instances of severe violence were identified in the clinical population. When correlated with MOAS scores, these had a wider standard deviation than lower severity scores.

3.1.8. Crime and Violence Scale

The Crime and Violence Scale (CVS) (Conrad, Riley, Conrad, Chan, & Dennis, 2010) is a 31-item self-report measure of the frequency of violent conflict resolution strategies used, and interpersonal violence committed during the past year. The scale is composed of four conceptually distinct subscales: General Conflict Tactic Scale (GCTS), Property Crime Scale, Interpersonal Crime Scale, and Drug Crime Scale. Each item is dichotomously rated as either 0 (none) or 1 (occurred 1 or more times), and a summed total made for the overall score. In this study, the scale showed adequate reliability (0.76 for adult males and 0.72 for females) (Conrad et al., 2010). Further studies have also found the CVS to have good predictive validity in adolescent populations (White, 2005).

3.1.9. Attempted and Actual Assault Scale

The Attempted and Actual Assault Scale (attacks) (Bowers et al., 2007) is an attempt to measure interpersonal physical violence in detail. Different scores are given depending on the type of weapon chosen (1–6), the area of the body targeted (1–5) and intensity of the act

(1–2). In addition, ratings of the "assailants' commitment" and an estimate of overall injury potential are rated on a Visual Analogue Scale (VAS) and contribute to the overall severity rating. This involves placing a cross along a line from "zero" to "total" and "no injury" to "serious" to rate level of commitment and potential injury respectively. It is designed to be rated by nurses and intended for inpatient settings. Inter-rater reliability was 0.7, better than for MOAS severity scores in this study (Bowers et al., 2007); however, the validity is untested. The attacks form are easy to complete but interpreting it is more complicated as ratings on a VAS require measurement with a ruler of distances from an anchor point. To our knowledge, this tool has been used in only one study of a population with acquired brain injury (Dickens, Alderman, & Bowers, 2011).

3.2. Methods used in previous research

Previous studies of aggression and violence in those with mental disorders have varied in their approaches employed, but also in the methods of categorization, in terms of where thresholds for dichotomization of violence exist. Some studies dichotomized on the basis or absence of a history of violent conduct, without providing details of the threshold used. Other researchers have made explicit their definitions of violence; however these definitions of what constitutes violence have varied across studies. Examples of some definitions used in studies of mental illness and violence are shown in Table 1. A smaller number of studies have moved beyond a simple definition of violence based on categories of behaviors, and have used the assessment tools described above to allow a richer description of the violent behavior.

4. Discussion

The nature of the link between violent behavior and mental illness is complex, and research with patients with mental illness should not be reduced to verifying whether a patient did or did not commit a violent act during the period in question because this will not provide rich enough information to generate confidence in whatever results are obtained (Mulvey & Lidz, 1993). All the methods of measurement discussed above have their own strengths and limitations as summarized in Fig. 1. Therefore, the challenge for researchers is to devise a set of assessments that will best measure a patient's violent behavior.

The most comprehensive way of determining a history of violence is to use multiple sources of information, such as self-report, convictions, and information from a relative. These sources should be incorporated into the method of measurement, for example assessing both self-report and official records and using both sources of information to make the measure. This measure should be structured in order to allow systematic collection of data and validity when used across samples. This could be achieved by the use of descriptors, anchor points, or Likert scales. It is also likely to be beneficial to use a method of assessment which allows consideration of both frequency and severity of the violent behavior and potentially planning and intent.

As discussed above, it has been argued that such measures should not be contingent on the outcome of the behavior. However, despite using more sophisticated methods of assessing violence, it is likely that studies will seek to categorize patients as violent or non-violent due to not having sufficiently sized samples to analyze smaller sub-groups. Utilizing a scale of a range of histories of violent behavior will only be possible in large samples, which poses a considerable recruitment challenge in this difficult to recruit population.

5. Conclusion

Despite the global nature of violence, and a wealth of research, its quantification still poses a significant research challenge. Broadly speaking, studies have attempted to quantify violence across several

Table 1
Categorization of violence used in previous studies of schizophrenia and violence.

Author	Categorization of violence
De Sanctis et al. (2012)	Physical assault in last year, LHA score of 20 or more and score of 3 or more on physical aggression against people sub-scale
Gregory et al. (2012)	Violent offenders (rape, murder, attempted murder, grievous bodily harm)
Schiffer et al. (2012)	Grouped by presence of violent offence (LHA used as a variable)
Dumais et al. (2011)	Lifetime history of murder, attempted murder or wounding
Dolan and Fullam (2009)	Convicted of violent offence
Elbogen and Johnson (2009)	Lifetime history of assault causing injury, rape, arson, weapon use
Puri et al. (2008)	Murder, attempted murder, wounding with intent to do grievous bodily harm
Tiihionen et al. (2008)	Violent offences (murder, armed robbery, assaults)
Hodgins et al. (2007)	MacArthur Community Violence Instrument Record of convictions Simple battery and above as in Swanson et al. (2006)
Swanson et al. (2006)	MacArthur Community Violence Instrument (minor violence was simple battery, major violence defined as any assault with lethal weapon or causing injury, threat with a lethal weapon in hand or sexual assault)
Coid et al. (2006)	Having been in a physical fight, assaulted or deliberately hit anyone in the last five years
Abushua'leh and Abu-Akel (2006)	Minimum of three assaults against others (multiple sources of information)
Barkataki et al. (2005)	Gunn Robertson scales (lifetime and index offence) score of 5 indicating fatal or near fatal act of violence and one other moderately serious incident of violence
Buckley et al. (2004)	Act of physical aggression against person or property that incurred legal charges
Stompe et al. (2004)	Low violence = sexual assault, robbery, threats with a weapon, severe damage to property High violence = grievous bodily harm, murder, attempted murder, arson with intent
Arseneault et al. (2000)	Two different self-reported violent incidents in past year or one convicted violent offence in past five years
Appelbaum et al. (2000)	Batteries that resulted in injury or involved the use of a weapon; sexual assaults; threats made with a weapon in hand
Arango et al. (1999)	Score of more than 2 on OAS for physical aggression
Lachman et al. (1998)	Multiple assaults
Wong et al. (1993)	Measures used as in Taylor (1985)
Taylor (1985)	Gunn-Robertson scale for lifetime violence and modified version for current violent offence

Method	Advantages	Disadvantages
Self-report	Likely to reveal the highest rates of violent behavior. Easy and convenient.	No corroboration
Record of convictions	Reliable and easily comparable between participants	Underestimates the amount of violent behavior as some will be undetected by the authorities
Lifetime History of Aggression	Considers prevailing pattern over lifetime	Does not consider more severely violent behavior
Modified Overt Aggression Scale	Observed behavior rated contemporaneously	Groups diverse behaviors together Does not differentiate outcome and severity
Gunn Robertson scale	Considers self-reported violence, convictions and medical records	One rating entirely dependent on convictions
Quantification of Violence Scale	Can be used for severe violence	Numerical version difficult to score, intent/planning scores difficult to judge/collect
MacArthur Community Violence Instrument	Considers self-report and informant information	Mainly used as a dichotomous tool, despite potential for distinct items to be better classified
Liverpool Violence Assessment	Distinguishes severity and frequency Accounts for associated factors	Information gained through interview only
Violence Scale	Likert scale instead of simple dichotomised scaling Easy to administer in clinical environments	Designed to be completed by nurses observing in-patients
Crime and Violence scale	Considers a wide range of crimes in addition interpersonal violence	Better construct validity in adolescents than adults
Attacks	Easy to complete form and comprehensive consideration of relevant factors	Interpretation can seem complex and requires measurement with a ruler

Fig. 1. Advantages and disadvantages of different measures of history of violence.

different dimensions; however, due to the complex and variable nature of violence, and methodological limitations, many of these measures remain largely unvalidated across populations. Data on violent acts are difficult to collect and are often done so retrospectively with a reliance on self-report measures. One of the main difficulties facing researchers is the need for large sample sizes in order to validate measures, while still preserving the richness of collected data. Despite this, future studies should move away from simply defining violence to quantification using multiple sources and taking into consideration different dimensions of violence.

Role of funding source

None.

Appendix A. Example of systematic search strategy — Scopus

Search terms	No of studies
"Violence scale"	99
"Violence measure"	37
"Violence tool"	4
"Violence assessment"	73
"Violence rating"	33
"Assessment of violence"	94
"Measurement of violence"	11
"Quantif* violence"	3
"Quantification of violence"	1
"Violence quantification"	0

References

Abushua'leh, K., & Abu-Akel, A. (2006). Association of psychopathic traits and symptomatology with violence in patients with schizophrenia. *Psychiatry Research, 143*(2–3), 205–211.

Anderson, C. A., & Bushman, B. J. (2002). Human aggression. *Annual Review of Psychology, 53*, 27–51.

Appelbaum, P., Robbins, P., & Monahan, J. (2000). Violence and delusions: Data from the MacArthur violence risk assessment study. *The American Journal of Psychiatry, 157*, 566–572.

Arango, C., Barba, A., Gonzalez-Salvador, T., & Ordonez, A. (1999). Violence in inpatients with schizophrenia: A prospective study. *Schizophrenia Bulletin, 25*, 493–503.

Arseneault, L., Moffitt, T., Caspi, A., Taylor, P., & Silva, P. (2000). Mental disorders and violence in a total birth cohort: Results from the Dunedin study. *Archives of General Psychiatry, 57*, 979–986.

Barkataki, I., Kumari, V., Das, M., Hill, M., Morris, R., O'Connell, P., et al. (2005). A neuropsychological investigation into violence and mental illness. *Schizophrenia Research, 74*, 1–13.

Bowers, L. (1999). A critical appraisal of violent incident measures. *Journal of Mental Health, 8*(4), 339–349. http://dx.doi.org/10.1080/09638239917265.

Bowers, L., Nijman, H., & Palmstierna, T. (2007). The Attempted and Actual Assault Scale (attacks). *International Journal of Methods in Psychiatric Research, 16*(3), 171–176.

Buckley, P. F., Hrouda, D. R., Friedman, L., Noffsinger, S. G., Resnick, P. J., & Camlin-Shingler, K. (2004). Insight and its relationship to violent behavior in patients with schizophrenia. *The American Journal of Psychiatry, 161*(9), 1712–1714.

Butchart, A., Phinney, A., Check, P., & Villaveces, A. (2004). *Preventing violence: A guide to implementing the recommendations of the world report on violence and health*. Geneva: World Health Organization.

Cerda, M., DiGangi, J., Galea, S., & Koenen, K. C. (2012). Epidemiologic research on interpersonal violence and common psychiatric disorders: Where do we go from here? *Depression and Anxiety, 29*, 359–385.

Coccaro, E. F., Berman, M. E., & Kavoussi, R. J. (1997). Assessment of life history of aggression: Development and psychometric characteristics. *Psychiatry Research, 73*(3), 147–157. http://dx.doi.org/10.1016/s0165-1781(97)00119-4.

Coid, J., & Yang, M. (2011). The impact of psychopathy on violence among the household population of Great Britain. *Social Psychiatry and Psychiatric Epidemiology, 46*(6), 473–480.

Coid, J., Yang, M., Roberts, A., Ullrich, S., Moran, P., Bebbington, P., et al. (2006). Violence and psychiatric morbidity in a national household population — A report from the British household survey. *American Journal of Epidemiology, 164*(12), 1199–1208.

Conrad, K. J., Riley, B. B., Conrad, K. M., Chan, Y. -F., & Dennis, M. L. (2010). Validation of the Crime and Violence Scale (CVS) against the Rasch measurement model including differences by gender, race, and age. *Evaluation Review, 34*(2), 83–115. http://dx.doi.org/10.1177/0193841x10362162.

De Sanctis, P., Foxe, J., Czobor, P., Wylie, G., Kamiel, S., Huening, J., et al. (2012). Early sensory–perceptual processing deficits for affectively valenced inputs are more pronounced in schizophrenia patients with a history of violence that their non-violent peers. *Social Cognitive and Affective Neuroscience*. http://dx.doi.org/10.1093/scan/nss052.

Dickens, G., Alderman, N., & Bowers, L. (2011). Potential severity of aggressive behaviour after acquired brain injury: Implications for recording. *Journal of Psychiatric and Mental Health Nursing, 18*, 587–594.

Dolan, M., & Fullam, R. (2009). Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. *Biological Psychiatry, 66*, 570–577.

Douglas, K. S., Guy, L. S., & Hart, S. D. (2009). Psychosis as a risk factor for violence to others: A meta-analysis. *Psychological Bulletin, 135*(5), 679–706.

Dumais, A., Potvin, S., Joyal, C., Allaire, J. -F., Stip, E., Lesage, A., et al. (2011). Schizophrenia and serious violence: A clinical-profile analysis incorporating impulsivity and substance-use disorders. *Schizophrenia Research, 130*(1–3), 234–237. http://dx.doi.org/10.1016/j.schres.2011.02.024.

Elbogen, E., & Johnson, S. (2009). The intricate link between violence and mental disorder: Results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry, 66*, 152–161.

Fazel, S., Langstrom, N., Hjern, A., Grann, M., & Lichtenstein, P. (2009). Schizophrenia, substance abuse and violent crime. *JAMA: The Journal of the American Medical Association, 301*, 2016–2023.

Gregory, S., Simmons, A., Kumari, V., Howard, M., Hodgins, S., & Blackwood, N. (2012). The antisocial brain: Psychopathy matters: A structural MRI investigation of antisocial male violent offenders. *Archives of General Psychiatry, 69*(9), 962–972.

Gunn, J., & Robertson, G. (1976). Drawing a criminal profile. *British Journal of Criminology, 16*(2), 156–160.

Hodgins, S., Alderton, J., Cree, A., Aboud, A., & Mak, T. (2007). Aggressive behaviour, victimisation and crime among severely mentally ill patients requiring hospitalisation. *The British Journal of Psychiatry, 191*(OCT.), 343–350.

Hoptman, M., D'Angelo, D., Catalano, D., Mauro, C., Shehzad, Z., Kelly, A., et al. (2010). Amygdalofrontal functional disconnectivity and aggression in schizophrenia. *Schizophrenia Bulletin, 36*, 1020–1028.

Hoptman, M., Volavka, J., Johnson, G., Weiss, E., Bilder, R., & Lim, K. (2002). Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: A preliminary study. *Biological Psychiatry, 52*, 9–14.

Kay, S. R., Wolkenfeld, F., & Murrill, L. M. (1988). Profiles of aggression among psychiatric patients. I. Nature and prevalence. *The Journal of Nervous and Mental Disease, 176*(9), 539–546.

Krakowski, M. I., & Czobor, P. (2012). The denial of aggression in violent patients with schizophrenia. *Schizophrenia Research, 141*(2–3), 228–233.

Krug, E. G. (2002). *World report on violence and health: Summary*. Geneva: World Health Organization.

Krug, E. G., Mercy, J. A., Dahlberg, L. L., & Zwi, A.B. (2002). The world report on violence and health. *The Lancet, 360*(9339), 1083–1088. http://dx.doi.org/10.1016/S0140-6736(02)11133-0.

Kumari, V., Das, M., Taylor, P., Barkataki, I., Andrew, C., Sumich, A., et al. (2009). Neural and behavioural responses to threat in men with a history of serious violence and schizophrenia or antisocial personality disorder. *Schizophrenia Research, 110*, 47–58.

Lachman, H., Nolan, K., Mohr, P., Saito, T., & Volavka, J. (1998). Association between catechol O-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder. *American Journal of Psychiatry, 155*, 835–837.

McGregor, K., Castle, D., & Dolan, M. (2012). Schizophrenia spectrum disorders, substance misuse and the four-facet model of psychopathy: The relationship to violence. *Schizophrenia Bulletin, 136*, 116–121.

Meehan, J., Flynn, S., Hunt, I., Robinson, J., Bickley, H., Parsons, R., et al. (2006). Perpetrators of homicide with schizophrenia: A national clinical survey in England and Wales. *Psychiatric Services, 57*, 1648–1651.

Michie, C., & Cooke, D. J. (2006). The structure of violent behavior: A hierarchical model. *Criminal Justice and Behavior, 33*(6), 706–737. http://dx.doi.org/10.1177/0093854806288941.

Morrison, E. (1993). The measurement of aggression and violence in hospitalized psychiatric patients. *International Journal of Nursing Studies, 30*, 51–64.

Mulvey, E. P., & Lidz, C. W. (1993). Measuring patient violence in dangerousness research. *Law and Human Behavior, 17*(3), 277–288.

Nathan, R., Rollinson, L., Harvey, K., & Hill, J. (2003). The Liverpool Violence Assessment: An investigator-based measure of violence. *Criminal Behaviour and Mental Health, 13*, 106–120.

Nolan, K. A., Volavka, J., Czobor, P., Sheitman, B., Lindenmayer, J. P., Citrome, L. L., et al. (2005). Aggression and psychopathology in treatment-resistant inpatients with schizophrenia and schizoaffective disorder. *Journal of Psychiatric Research, 39*(1), 109–115.

Puri, B., Counsell, S., Saeed, N., Bustos, M., Treasaden, I., & Bydder, G. (2008). Regional grey matter volumetric changes in forensic schizophrenia patients: An MRI study comparing the brain structure of patients who have seriously and violently offended with that of patients who have not. *BMC Psychiatry, 8*(Suppl. 1), 56.

Schiffer, B., Leygraf, N., Muller, B., Scherbaum, N., Forsting, M., Wiltfang, J., et al. (2012). Structural brain alterations associated with schizophrenia preceded by conduct disorder: A common and distinct subtype of schizophrenia? *Schizophrenia Bulletin*. http://dx.doi.org/10.1093/schbul/sbs115.

Serper, M. R. (2011). Aggression in schizophrenia. *Schizophrenia Bulletin, 37*(5), 897–898. http://dx.doi.org/10.1093/schbul/sbr090.

Steadman, H. J., Mulvey, E. P., Monahan, J., Robbins, P. C., Appelbaum, P.S., Grisso, T., et al. (1998). Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. *Archives of General Psychiatry, 55*(5), 393–401.

Stompe, T., Ortwein-Swoboda, G., & Schanda, H. (2004). Schizophrenia, delusional symptoms, and violence: Threat/control-override concept re-examined. *Schizophrenia Bulletin, 30*, 31–44.

Swanson, J., Swartz, M., Van Dorn, R., Elbogen, E., Wagner, H., Rosenheck, R., et al. (2006). A national study of violent behaviour in persons with schizophrenia. *Archives of General Psychiatry, 63*, 490–499.

Swanson, J., van Dorn, R., Swartz, M., Smith, A., Elbogen, E., & Monahan, J. (2008). Alternative pathways to violence in persons with schizophrenia: The role of childhood antisocial behaviour problems. *Law and Human Behavior, 32*, 228–240.

Taylor, P. J. (1985). Motives for offending among violent and psychotic men. *The British Journal of Psychiatry, 147*(NOV.), 491–498.

Teplin, L. A., McClelland, G. M., Abram, K. M., & Weiner, D. A. (2005). Crime victimization in adults with severe mental illness: Comparison with the national crime victimization survey. *Archives of General Psychiatry, 62*(8), 911–921.

Tiihonen, J., Rossi, R., Laakso, M., Hodgins, S., Testa, C., Perez, J., et al. (2008). Brain anatomy of persistent violent offenders: More rather than less. *Psychiatry Research: Neuroimaging, 163*, 201–212.

Tyrer, P., Cooper, S., Herbert, E., Duggan, C., Crawford, M., Joyce, E., et al. (2007). The quantification of violence scale: A simple method of recording significant violence. *The International Journal of Social Psychiatry, 53*(6), 485–497. http://dx.doi.org/10.1177/0020764007083870.

Walsh, E., Buchanan, A., & Fahy, T. (2002). Violence and schizophrenia: Examining the evidence. *The British Journal of Psychiatry, 180*, 490–495.

Webster, C., Douglas, K., Eaves, D., & Hart, S. (1997). *HCR-20: Assessing risk for violence (version 2)*. Vancouver: Simon Fraser University.

White, M. (2005). Predicting violence in juvenile offenders: The interaction of individual, social and environmental influences. *Offender Substance Abuse Report, 5*, 83–90.

Wong, M., Lumsden, J., Fenton, G., & Fenwick, P. (1993). Violence ratings of special hospital patients. *Journal of Forensic Psychiatry, 4*(3), 471–480.

Yu, R., Geddes, J. R., & Fazel, S. (2012). Personality disorders, violence, and antisocial behavior: A systematic review and meta-regression analysis. *Journal of Personality Disorders, 26*(5), 775–792.

Yudofski, S., Silver, J., Jackson, W., Endicott, J., & Williams, D. (1986). The Overt Aggression Scale for the objective rating of verbal and physical aggression. *The American Journal of Psychiatry, 143*, 35–39.

3.2 Validity and reliability of tools

The measures of inter-rater reliability and concurrent validity of the tools described in the published paper above are summarised in table 3-1 below.

Table 3-1 Reliability and validity of violence measurement tools

Violence measurement tool	Inter-rater reliability	Concurrent validity
Gunn Robertson Scale (Gunn and Robertson, 1976)	0.92	Value not reported
Modified Overt Aggression Scale (Kay et al., 1988)	Between 0.85 and 0.94	Value not reported
Violence Scale (Morrison, 1993)	0.69	Value not reported
Lifetime History of Aggression (Coccaro et al., 1997)	0.95	0.45
MacArthur Community Violence Instrument (Steadman et al., 1998)	Value not reported	Value not reported
Liverpool Violence Assessment (Nathan et al., 2003)	0.96	0.41
Quantification of Violence Scale (Tyrer et al., 2007)	0.69	0.67
Actual and Attempted Assault Scale (Bowers et al., 2007)	0.7	0.7
Crime and Violence Scale (Conrad et al., 2010)	Between 0.72 and 0.76	Value not reported

3.3 Conclusions

As a result of this systematic review, we concluded that the Gunn Robertson Violence Scale (Gunn and Robertson, 1976), was the most appropriate tool to utilise in this study. This decision was based on its excellent inter-rater reliability, that it assessed information from both self-report and official records, and that it was a five-point scale which allows for assessment of a range of severities of violent behaviour.

Chapter 4 Methodology

4.1 Abstract

This chapter describes the general methodology for the study, including recruitment of participants, clinical assessments undertaken and statistical analyses.

4.2 Aims

This study aimed to identify and define the clinical correlates underlying violent behaviour in schizophrenia. It specifically sought to examine the putative role of childhood adversities, conduct disorder and co-morbid substance misuse. On the basis of the existing literature, in order to define more precisely the factors that predispose to violence in men with schizophrenia, recruited patients were assessed for symptoms of prior conduct disorder in addition to their history of violence. The study aimed to recruit patients from a wide range of mental health settings, including outpatients and inpatients in both secure and non-secure units.

While the link between schizophrenia and violence is clear (see chapter 2); at present we understand very little about which patients with schizophrenia will behave violently and under what circumstances, so prediction and prevention is challenging, but a vital public health and human rights issue. Therefore, the longer term objective is that the results of this study will inform future developments in the assessment of the risk of violence in schizophrenia and improve the treatment of these patients to reduce the risk of violence.

4.3 Ethical approval

The Birmingham East, North and Solihull NHS Research Ethics Committee approved the study in December 2010. Three substantial amendments were later approved in July and October 2011 and February 2012. Minor amendments were also approved in February 2011 and March 2014. NHS Research & Development approval was obtained for each recruiting NHS trust:

- Birmingham and Solihull Mental Health NHS Foundation Trust (August 2011)

- Northamptonshire Healthcare NHS Foundation Trust (December 2011)
- Oxford Health NHS Foundation Trust (May 2012)
- Leicestershire Partnership NHS Trust (September 2012)

Local Research & Development approval was obtained for one non-NHS site (St Andrew's Healthcare – Northampton, Birmingham and Essex sites).

4.4 Power calculation

I conducted a power calculation under the supervision of the Biostatistics Department at the Institute of Psychiatry, Psychology and Neuroscience using G*Power 3 (Faul et al., 2007). A power calculation provides an estimate of an adequate sample size to detect the effects hypothesised in the study. Similar studies with the same dependent variable were identified but none had utilised the five-point scale of the Gunn Robertson Violence Scale. Therefore, it was necessary to consider studies using the presence or absence of violence instead in order to undertake the power calculation. A study with the required clinically significant effect sizes and reported standard deviations was identified following advice from the Biostatistics Department; the calculation used primary outcome data from Arango et al. (1999) for prediction of violence in patients with schizophrenia with positive psychotic symptoms. Analysis of Variance at the 0.05 significance level would have 80% power to detect a significant difference in Positive and Negative Syndrome Scale (Kay et al., 1987) positive psychotic symptoms scores between patients with schizophrenia with and without a history of violence (difference in means 5.5 and parsimoniously assuming a common standard deviation of 6), with a total sample of 60 subjects. Therefore this study aimed to recruit 60 men with schizophrenia.

4.5 Participants

4.5.1 Inclusion criteria

Inclusion criteria for all participants were:

- male
- between 18 and 65 years
- fluent in English

Additionally for patients, they had:

- a primary diagnosis of schizophrenia
- capacity to consent to participate

4.5.2 Exclusion criteria

Participants were excluded if they had a:

- history of epilepsy
- history of significant head injury (loss of consciousness for more than 3 minutes or requiring hospitalisation)
- learning/intellectual disability or dementia
- history of neurological disorder
- current active substance abuse/dependence
- history of mania or hypomania

4.5.3 Recruitment

Patients with schizophrenia were recruited from four large NHS Mental Health Trusts: Birmingham and Solihull Mental Health NHS Foundation Trust, Northamptonshire Healthcare NHS Foundation Trust, Oxford Health NHS Foundation Trust and Leicestershire Partnership NHS Trust. Each Trust provides general adult and forensic psychiatric services to working age adults in their respective catchment areas. Each Trust was considered to offer representative sampling of male patients with schizophrenia, as they offered secondary and tertiary mental healthcare services for patients with schizophrenia in their respective catchment areas. Recruitment included one independent organization that cared for NHS patients, St Andrew's Healthcare with hospitals in Essex, Northampton and Birmingham. Potential candidates were identified by their Responsible Clinicians and once they agreed were referred to the study.

Healthy control participants were recruited from the local area by newspaper advertisements and posters and flyers in local shops and businesses. This aimed to recruit a representative sample of men in the general population without schizophrenia.

4.6 Clinical assessments

4.6.1 Schizophrenia

4.6.1.1 Diagnosis

The Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 2002) was used to diagnose schizophrenia and any mood disorders. This consisted of a structured clinical interview and review of the patients' medical records.

4.6.1.2 Symptoms

As part of the SCID-I assessment the lifetime presence of a range of psychotic symptoms was elicited. This was augmented by specific questions to identify any threat/control-override symptoms (Stompe et al., 2004). Threat symptoms are clear, unequivocal persecutory delusions that impose a feeling of imminent danger on the patient. Control-override symptoms are passivity phenomena comprising external interference. Psychotic symptoms at the time of the assessment were evaluated using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). This widely used scale comprises 7 items relating to positive symptoms of psychosis (e.g. delusions), 7 items relating to negative symptoms (e.g. emotional withdrawal) and 16 items relating to general psychopathology (e.g. anxiety). All 30 items are rated on a 7 point scale from absent to extreme. Scores range from 7 to 49 for the positive and negative scales and 16 to 112 for the general psychopathology scale.

Patients' insight into their mental illness was assessed using the self-report Insight Scale (Birchwood et al., 1994). The scale considers three factors (awareness of illness, need for treatment and attribution of symptoms) by way of eight questions. The maximum score is 12, with 0 indicating no insight and 9 or above considered to represent good insight.

4.6.1.3 Current functioning

The Global Assessment of Functioning scale (GAF) from the SCID-I (First et al., 2002) was used to obtain a measure of the participant's overall social, occupational and psychological

functioning at the time of the assessment. It is an ordinal scale from 1-100 on a hypothetical continuum of mental illness-health. For example, the descriptor for the range 91-100 is '*Superior functioning in a wide range of activities, life's problems never seem to get out of hand, is sought out by others because of his many positive qualities. No symptoms*.' (First et al., 2002).

4.6.2 Conduct disorder, antisocial personality disorder and psychopathy

4.6.2.1 Conduct disorder and antisocial personality disorder

Conduct disorder (CD) and antisocial personality disorder (ASPD) were assessed using the Structured Clinical Interview for DSM-IV Axis II disorders (SCID-II) (First et al., 1997). DSM-IV requires the presence of some symptoms of CD in childhood or adolescence in order for a later diagnosis of ASPD to be made, in SCID-II this is operationalized as two symptoms of CD needing to be present to allow a diagnosis of adult ASPD to be made. However, three CD symptoms are needed for CD to be diagnosed itself (First et al., 1997). Therefore, in this study two symptoms of CD allowed an adult diagnosis of ASPD to be made but three symptoms were required for a retrospective diagnosis of CD to be made.

4.6.2.2 Psychopathy

The Psychopathy Checklist Screening Version (PCL:SV) (Hart et al., 1995) is a psychopathy screening tool which is robustly related to the full Psychopathy Checklist Revised (PCL-R) (Guy and Douglas, 2006). The PCL:SV was scored on the basis of an interview with the participant and review of their medical records. The PCL:SV has 12 items rated 0 (not present), 1 (possibly present), or 2 (definitely present), giving a total possible score of 24. The usual cut-off score for psychopathy is 18 (Guy and Douglas, 2006). I have received the necessary training to use the PCL-R and PCL:SV.

4.6.3 Alcohol and drugs

Lifetime substance use disorders were diagnosed using the SCID-I, which considers abuse and dependence on alcohol and various illicit drugs. An additional study specific questionnaire was designed to obtain more detailed information about substance use and how it may relate to violent behaviour (see appendix B). A bespoke questionnaire was employed,

rather than an existing one, because the questionnaires used in previous studies were to screen for substance misuse, whereas we could make a definitive diagnosis of such using the SCID-1. Therefore, the additional questions were to focus on use of substances in adolescence (to explore the potential relationship with conduct disorder and violence in line with my hypotheses) and any associations between substance misuse and violent behaviour. Our questionnaire included questions about the age of onset of use of each substance; the frequency of use before the age of 15 and before 18, and at its peak usage; and the quantity of the substance consumed at its peak usage. It also asked about whether participants had committed an alcohol or drug-related offence (e.g. drunk and disorderly or possession of drugs), whether they had stolen to buy the substance, whether they had ever been violent whilst intoxicated or whether they had been the victim of violence when intoxicated. In addition, the medical records of patient participants were reviewed for information regarding substance misuse.

4.6.4 Childhood adversity

The Childhood Experiences of Care and Abuse Questionnaire (CECA-Q) (Bifulco et al., 2005) rates retrospective reports of childhood maltreatment. It is reliable in individuals with psychotic disorders (Fisher et al., 2011). A briefer modified version of the CECA-Q was employed (Hepgul et al., 2012), in order to keep the overall duration of the assessment battery to a manageable length for participants.

4.6.5 Other clinical information

4.6.5.1 Demographics

Basic demographic information was obtained from participants including age, ethnicity, age of leaving full-time education and current employment status. For patients their Mental Health Act status and current placement were noted.

4.6.5.2 Family history of mental disorder

The Family Interview for Genetic Studies (FIGS), a structured instrument that gathers diagnostic information on patients' relatives (Maxwell, 1992) was conducted with all participants and, where possible, also with a family member.

4.6.5.3 Illness course

Past psychiatric history was obtained from the medical records including, age of illness onset, number and duration of hospital admissions and medication history. Specific information required to determine treatment resistance or remission was also collected from the patients' notes.

Remission was defined as no symptomatic relapses for a period of six months and the following PANSS items scored as mild (3) or less (Andreasen et al., 2005):

- Delusions (P1)
- Conceptual disorganization (P2)
- Hallucinatory behaviour (P3)
- Blunted affect (N1)
- Social withdrawal (N4)
- Lack of spontaneity (N6)
- Mannerisms/posturing (G5)
- Unusual thought content (G9)

Treatment resistance was determined using the modified Kane criteria (Conley and Kelly, 2001), adapted for use with the PANSS:

- At least two prior antipsychotic trials of 4-6 weeks duration at 400-600mg/day chlorpromazine equivalents with no clinical improvement
- Persistence of illness for more than 5 years with no period of social or occupational functioning
- Persistent psychotic symptoms assessed with PANSS as a score of moderate or greater on at least one of the positive psychotic symptom items (P items)

4.6.5.4 Medication

Patients' antipsychotic medication at the time of the assessment was converted to chlorpromazine equivalents using the best available data (Gardner et al., 2010) to allow comparison of doses of prescribed medication.

4.7 Assessment of violence

4.7.1 MacArthur Community Violence Instrument

All participants were asked about violent behaviour based on the MacArthur Community Violence Instrument (Steadman et al., 1998). It assesses whether the participant has:

- Thrown something at anyone
- Pushed, grabbed, or shoved
- Slapped
- Kicked, bitten or choked anyone
- Hit anyone with a fist, object or beaten anyone
- Physically forced someone to have sex against their will
- Threatened anyone with a weapon
- Used a weapon

Participants indicated how many times over their adult lifetime they had engaged in each type of aggressive behaviour and whether in the last six months they had perpetrated, or been a victim of, each behaviour. Collateral information about lifetime violent behaviour in each category was obtained from medical records (for patients), and family informants where available for all participants.

Responses to the question about forcing someone to have sex were not included in the analyses as this was a study of nonsexual violence, rather than sexual violence. Previous research suggested that disaggregating items on the MacArthur Community Violence Instrument (MCVI) into their component parts may improve measurement, particularly the question 'Have you kicked, bitten, or choked anyone?' as it appears to be a complex item containing disparate violent acts (Michie and Cooke, 2006). Therefore this question was split into three separate questions about each aggressive behaviour (kicking, biting and choking) for this study and analysed accordingly. The MCVI can assess both recent (Steadman et al., 1998) and lifetime violence (Michie and Cooke, 2006). When the aggressive behaviour has occurred frequently during a participant's adult life it can be difficult to assign this an exact frequency, this was noted in the development of the Life History of Aggression tool and led to

the following scale being used for measuring the frequency of aggressive behaviours (Coccaro et al., 1997):

0 = never happened

1 = only happened once

2 = happened a couple or a few times (e.g. 2-3)

3 = happened several times (e.g.4-9)

4 = happened many times (e.g. 10+)

5 = happened so many times that I couldn't give a number

Therefore, in this study, the above scale was used for each of the aggressive behaviours in the MCVI to allow categorisation of frequencies and comparison of these.

4.7.2 Additional questions

4.7.2.1 Most violent act

Participants identified their most serious violent act, answering the following questions:

- What is the most violent thing you've ever done?
- Why did you behave that way?
- What was the effect on you?
- What was the effect for others?
- Who was to blame?

This information was used to determine whether the violent act was reactive or instrumental in nature.

4.7.2.2 Forensic history

Participants were asked about any history with the criminal justice system and if so, the nature of that contact (arrest, charge, caution, conviction and any sentence received).

4.7.2.3 Family forensic history

Participants and family informants were asked about a family history of violent behaviour and criminal convictions (including non-violent offences) and any associated sentences. They were also asked about other violence not investigated by the police, including domestic violence between parental figures in their childhood household.

4.7.3 Gunn Robertson Violence Scale

In the MacArthur Violence Risk Assessment Study (Steadman et al., 1998), aggressive acts were divided into two categories for analyses: violence (battery that resulted in physical injury, sexual assaults, assaultive acts that involved the use of a weapon, or threats made with a weapon in hand) and other aggressive acts (battery that did not result in physical injury). In this study we sought to utilise a scale that captured broader descriptive data on each subject's propensity to violence and selected the Gunn Robertson Violence Scale (see chapter 3).

A criminal profile was devised based on nine types of offending behaviours, with scales for fraud, motoring, drink, relationship to drinking, drugs, financial gain, violence, sex and theft (Gunn and Robertson, 1979). The violence scale incorporates aspects of several facets of violence including severity, victim injury, and frequency. Ratings are made on a five point anchored scale (0-4), incorporating the offence itself, the consequence to the victim, and legal consequences for the perpetrator. As detailed in chapter 3, ratings are given as follows:

0 = No convictions. Never gets into fights

1 = No convictions. Evidence of minimal violence, i.e. occasional fights or damage to property

2 = One or two convictions for violence, or repeated acts of violence to person or property, none of which has caused serious damage to life or health

3 = Three or more convictions for violence

4 = One or more severely violent episodes in which someone's life or health has been seriously damaged

Each participant was rated using the Gunn Robertson Violence Scale (GRVS) based on their lifetime history of offending, using information from the MCVI and other collateral information.

4.7.4 Buss Perry Aggression Questionnaire

The Buss Perry Aggression Questionnaire (BPAQ) is a self-report measure of aggressive attitudes and a trait measure of individual differences in aggressive tendencies (Buss and Perry, 1992) that has been used widely in studies of violence among patients with a mental disorder (Krakowski and Czobor, 2012, Hoptman et al., 2010). The BPAQ consists of twenty-

one items rated by participants on a five point scale, where 1 is extremely uncharacteristic of the participant and 5 is extremely characteristic of them. The items are divided into four sub-scales: physical aggression (e.g. If somebody hits me, I hit them back), verbal aggression (e.g. I often find myself disagreeing with people), anger (e.g. I have trouble controlling my temper) and hostility (e.g. When people are especially nice to me I wonder what they want); which can be summed for a total score.

4.7.5 Official records

4.7.5.1 Medical records

Patients gave informed consent for access to their medical records. Records were examined to determine the frequency of aggressive behaviours (using the categories of the MacArthur Community Violence Interview as above) and any documentation relating to their most serious violent incident or criminal offences.

4.7.5.2 Police National Computer records

All participants were asked for their permission to obtain information about them held by the Ministry of Justice on the Police National Computer (PNC). This included data about any cautions or convictions received and sentences imposed. Permission to access PNC records for the study participants was obtained from the Association of Chief Police Officers Criminal Records Office (ACRO) in April 2011. Once recruitment of participants had been completed, a data sharing agreement was drawn up with the Ministry of Justice to ensure the safe sharing of this confidential information. Unfortunately, this process was ultimately unsuccessful (see table 4-1).

Table 4-1 Timeline showing process attempting to obtain permission to Police National Computer records for participants

Date	**Action**
11th January 2011	Application to PNC Information Access Panel (PIAP) for access to PNC records
2nd March 2011	Received confirmation that application was approved at PIAP meeting

14th April 2011	Information provided to National Policing Improvement Agency about our information security procedures
19th April 2011	Information security approved and confirmation that data transfer could proceed
20th May 2011	Data supply template provided by person A, Justice Statistics Analytical Services (JSAS), MoJ. They informed us that all PNC data will be provided in one complete list at the end of the study.
2011 - 2013	Data collection for study
2nd July 2013	Discussion with person B (Head of Data Improvement, Analysis and Linking, JSAS, MoJ) who stated that the permission granted in 2011 was no longer sufficient as the process had changed. Therefore he provided us with a data sharing agreement template to complete.
27th September 2013	Draft data sharing agreement sent to Legal Compliance Manager, King's College London
4th November 2013	Approval of data sharing agreement received from Legal Compliance Manager, King's College London
14th November 2013	Draft data sharing agreement sent to person B
3rd January 2014	Revised agreement and questions received back from person B
17th January 2014	Revised version sent back to person B
10th February 2014	Further queries received from person B
21st February 2014	Responded to say they would send the data sharing agreement to their legal department
March – August 2014	No response to emails to person B
30th September 2014	Emails to various other people in JSAS as no response from person B for several months but received no responses
24th October 2014	Called MoJ switchboard and then email received from Justice Data Lab at MoJ asking for further information about the work with person B
28th October 2014	Email from person C (Statistician, MoJ) apologizing that the request had 'slipped through the net when person B left'. They agreed to send on to their legal team for comments.

November 2014 – March 2015	No response to emails to person C
9th April 2015	Email from person D, Head of Data Improvement, Analysis and Linking team, JSAS to say that person C is currently on maternity leave and it 'looks like this has slipped through the cracks again'.
10th April 2015	Data sharing agreement and accompanying information send to person E (PNC Statistics Team)
13th April 2015	Request from person E for more information about why PNC data is essential for the study when self-report data has been collected. This was sent.
27th April 2015	Request for further information about the study protocol and recruitment. This was provided.
29th May 2015	Email from person E to state that the MoJ legal team were not satisfied that the PNC data was necessary/essential for the project and so would not agree to the data transfer.

4.8 Procedure

All participants were given a full description of the study's aims and design, and provided their written informed consent to take part. They were interviewed over at least two sessions, to complete the clinical assessments (approximately one and a half hours), and the neuropsychological and cognitive batteries (two to three hours with a colleague SH). Participants were given breaks as necessary. All interviews for in-patients were carried out on the patient's ward; for out-patients, the interviews were conducted at their out-patient clinic or at St Andrew's Hospital. All healthy controls were assessed at St Andrew's Hospital in Northampton. Ethically approved procedures were in place in case of unanticipated disclosures.

Participants were also asked to provide a urine sample for an illicit drug screen and have an MRI brain scan (lasting approximately 1 hour at Three Shires Hospital, Northampton). Where

consent was given, a family member was also contacted to provide collateral information. All participants were financially reimbursed (up to £55) for their time.

4.9 Statistical analyses

Statistical analyses were conducted using SPSS 18. All measures were assessed for normality. Where data were not normally distributed, or did not fit the assumptions for parametric analysis, non-parametric test equivalents were used. A significance level of $p<0.05$ was adopted throughout.

4.9.1 Between group comparisons

In order to test for differences between the patient and control groups for demographic and clinical variables, t-tests, Mann-Whitney U and chi-square analyses were used.

4.9.2 Analysis of violence

Ordinal logistic regression was used to determine whether measures were statistically significant predictors of violence in the patient group. These analyses were only conducted in the patient group due to the low levels of violence among control participants. The ordinal logistic regression was based on the proportional odds model, which assumes that the effect of the independent variable is the same for all splits of the categories of the outcome variable. The parameters of the proportional odds model represent the odds ratios of being in the highest categories compared to the lowest categories. For example, with the five outcome categories of the GRVS, and a single independent variable, then the odds ratio represents the combined comparison of outcome: category 4 with categories 3, 2, 1 and 0; categories 4 and 3 with categories 2, 1 and 0; categories 4, 3 and 2 with categories 1 and 0; categories 4, 3, 2 and 1 with category 0.

4.9.3 Co-linearity

Due to most variables not being normally distributed, Spearman's correlations were calculated in order to assess inter-relationships between variables.

4.9.4 Effect size

Odds ratios were calculated where appropriate, as it is widely recommended to report effect sizes even where results are not statistically significant.

4.9.5 Mediation analyses

Mediation analyses were carried out by testing the necessary triangle associations: statistically significant relationship between 1) independent and dependent variable; 2) independent and hypothesized mediator variable; 3) mediator and dependent variable. Substantial attenuation in magnitude of effect of the association between independent and dependent variable after covariation of the mediator variable was interpreted as an indirect pathway (Ullrich et al., 2014).

Chapter 5 Conduct Disorder and Quantification of Violence

5.1 Abstract

This chapter characterizes the study sample, assesses the validity of the Gunn Robertson Violence Scale to measure violence and considers the role of conduct disorder in lifetime violent behaviour among men with schizophrenia. The results demonstrate that the GRVS has good construct validity and reasonable concurrent validity. Conduct disorder, antisocial personality disorder and Psychopathy Checklist Screening Version score are all associated with the Gunn Robertson Violence Scale after controlling for substance use disorders. Those patients with pre-morbid conduct disorder more frequently engaged in all types of violent behaviours assessed, apart from choking, indicating conduct disorder is a significant factor influencing later propensity to violence. Aggressive attitudes were not associated with violence after relevant adjustments, either in all participants or the patient group only. However, pre-morbid conduct disorder was associated with aggressive attitudes in adulthood, apart from the hostility sub-scale which was associated with current psychotic symptoms. Instrumental violence was associated with higher psychopathy score.

5.2 Background

Our systematic review in chapter 3 (Harris et al., 2013), led to the selection of the Gunn Robertson Violence Scale (GRVS) as the method of quantifying violence in this study. The GRVS was selected on the basis of three primary strengths: firstly, it incorporates data on both criminal justice interventions as well as self-reported violent incidents that remain undetected by the police or courts; secondly, that it considers severity, frequency and impact of violence; and finally, that several categories of violence (rather than dichotomous categories) could be utilized in the analyses.

Traditionally, two forms of violence have been described, reactive and instrumental, although it is increasingly recognised that many individuals have a mixed pattern of violence (Dolan, 2010). Reactive violence is seen as provoked by a situation and is often emotionally charged. Instrumental violence is a premeditated means of obtaining a goal and is proactive rather than

reactive (Anderson and Bushman, 2002). Psychopathy is particularly associated with instrumental violence (Gregory et al., 2012), while ASPD may be more associated with reactive violence (Dolan, 2010). Instrumental violence occurs in some patients with schizophrenia and is usually associated with co-morbid psychopathy (Bo et al., 2011). Although interestingly, violence in the context of hallucinations and delusions can also sometimes be considered as instrumental (Felthous, 2008).

The literature relating to schizophrenia and violence and premorbid CD, co-morbid ASPD and psychopathy, is reviewed in section 2.4. To recap, CD is over-represented in patients with schizophrenia (Hodgins et al., 2008, Kim-Cohen et al., 2003) and is associated with an increased risk of violent behaviour (Arseneault et al., 2000, Hodgins et al., 2008, Swanson et al., 2008). People with ASPD and schizophrenia also have an increased risk of violence (Volavka, 2014, Bo et al., 2013). Psychopathy among those with schizophrenia is associated with lifetime violence and other criminal offending (McGregor et al., 2012, Tengström et al., 2004, Tengström et al., 2000).

Exploration of the relative importance of state versus trait factors in violence in schizophrenia is longstanding (Cheung et al., 1997a). The Buss Perry Aggression Questionnaire (BPAQ) is a trait measure of individual differences in aggressive tendencies (Buss and Perry, 1992) that has been used widely in studies of violence among patients with a mental disorder (Krakowski and Czobor, 2012, Hoptman et al., 2010). Anger has been described as the bridge to the verbal and physical aggression sub-scales of the BPAQ (Buss and Perry, 1992) and anger has consistently been shown to be associated with violence in the general population (Anderson and Bushman, 2002). Aggressive traits are a feature of CD (Blair et al., 2014) and it is possible that these remain longstanding into adulthood. Therefore trait aggression may differ in patients with schizophrenia on the basis of premorbid CD.

It has been suggested that the presence of CD is a crucial contributory factor in a typology of adult patients with schizophrenia who behave violently (see chapter 2). Violence among patients with schizophrenia may follow at least two distinct pathways, one associated with premorbid conditions, including CD, and another linked with the acute psychotic symptoms of schizophrenia (Volavka, 2014, Bo et al., 2011, Volavka and Citrome, 2011, Hodgins et al.,

2014, Van Dongen et al., 2014, Van Dongen et al., 2015). Therefore, this study specifically grouped patients on the basis of pre-morbid CD, in order to explore any differences between patients with schizophrenia, with and without pre-morbid CD, and how this affected their lifetime propensity to violence.

5.3 Hypotheses

This chapter will test the following hypotheses among men with schizophrenia:

1) The Gunn Robertson Violence Scale (GRVS) is a valid measure of lifetime propensity to violence
2) There is a cumulatively greater propensity for violence associated with:
    a. Each additional symptom of conduct disorder (CD)
    b. Each additional symptom of antisocial personality disorder (ASPD)
    c. Each additional item score of the Psychopathy Checklist Screening Version (PCL:SV)
3) More aggressive attitudes are associated with a greater propensity for violence
4) CD before the age of fifteen years old is associated with having more aggressive attitudes as an adult
5) Instrumental violence is associated with co-morbid psychopathy

5.4 Specific methodology

The general methodology is described in chapter 4, methodology relating specifically to this chapter concerns assessing whether the GRVS is a valid measure of lifetime propensity to violence. There are two main categories of validity used to assess a test or measure: content-related validity and criterion-related validity. Construct validity is a type of content-related validity and assesses whether the test or measure is related to underlying theoretical concepts. Construct validity was assessed by analysing associations between the GRVS and other constructs with well-established associations with violence (conduct disorder, antisocial personality disorder, psychopathy, prison sentences). Concurrent validity is a type of criterion-related validity and assesses whether it is related to an existing similar measure. Concurrent validity was tested by comparing the GRVS to the categories of severity of violence used in studies utilising the MacArthur Community Violence Instrument (MCVI), an established

benchmark measure. These categories were violence (battery that resulting in physical injury, sexual assaults, assaultive acts that involved the use of a weapon, or threats made with a weapon in hand) or other aggressive acts (battery that did not result in physical injury) (Steadman et al., 1998). All study participants were categorised using this method, in addition to the GRVS.

5.5 Specific statistical analyses

The general statistical analyses are described in chapter 4. Due to the number of comparisons in the analyses in this chapter, corrections for multiple testing were undertaken using the Bonferroni Hochberg method (Hochberg and Benjamini, 1990), as it is more powerful than the standard Bonferroni method and usually results in a conservative p-value adjustment. Both unadjusted and adjusted p–values are quoted.

5.6 Results

5.6.1 Inter-rater reliability

A colleague (SH) and I (CO) each independently rated all participants, on the basis of all information obtained from the interviews, family members and medical records, using the GRVS criteria. Inter-rater reliability was 89.4% across all participants. In the eleven cases of disagreement, we reviewed and discussed the evidence to reach a consensus. Differences in ratings, were principally due to differences in interpretation of the items, for example what constitutes ‘serious damage’ to health (rating = 4) and ‘occasional’ versus ‘repeated’ acts of violence (ratings = 1 and 2).

5.6.2 Adjustment for confounders

Age, ethnicity, Full Scale Intelligence Quotient (FSIQ) and current psychotic symptoms were considered as potential confounders based on the existing literature. However, in this sample of patients with schizophrenia, there were no associations between violence and age, ethnicity, FSIQ or PANSS score (total or sub-scales). Therefore, these variables were not adjusted for in the regression analyses.

A lifetime history of a substance use disorder was associated with lifetime propensity to violence (GRVS score) and so was included in all analyses. Symptoms of CD and ASPD, and PCL:SV score were all independently associated with the GRVS score in this sample. There was moderate correlation between symptoms of conduct disorder, symptoms of antisocial personality disorder and PCL:SV score as shown in the correlation table (see table 5-1), suggesting a degree of co-linearity.

PCL:SV score was the most strongly associated with GRVS score, and was added to the regression model first. In DSM-IV, prior CD symptoms are a pre-requisite for a diagnosis of ASPD, thus they were considered to be intimately related clinical constructs and only CD symptoms were entered into the regression models. However, adding CD symptoms in addition to PCL-SV score to the models did not significantly improve the model fit. Therefore, only a lifetime history of substance use disorders and PCL-SV score were included in the subsequent models.

5.6.3 Demographics

Ninety-three male participants were recruited for the study, fifty-four with schizophrenia and thirty-nine healthy controls with no history of any form of psychotic illness. As per the study's exclusion criteria, no participant had ever experienced a manic episode. One patient met criteria for a co-morbid depressive episode at the time of the assessment and nine other patients had experienced a previous depressive episode. Nine controls had a history of depression.

The patients were recruited from the full spectrum of inpatient and outpatient mental health services and all of the healthy controls were living in the local community. The ages of the participants ranged from eighteen to fifty-seven years old. All of the healthy controls, apart from one, were from a white background**.** Thirty-four of the patients were white British, six were white and black Caribbean, six were black Caribbean, five were Asian and three were of other ethnic backgrounds.

Table 5-1 Correlations with propensity to violence among patients (n=54)

	Correlation	GRVS	Age	Total duration in hospital	Total duration in prison	Number of CD symptoms	Number of ASPD symptoms	PCL:SV score	Total PANSS score	FSIQ
GRVS	r p		.01 0.954	.52 **<0.001**	.56 **<0.001**	.55 **<0.001**	.59 **<0.001**	.68 **<0.001**	-.08 0.555	-.15 0.304
Age	r p	.01 0.954		.52 **<0.001**	-.06 0.682	-.01 0.963	.02 0.901	.01 0.966	.17 0.224	-.07 0.623
Total duration in hospital	r p	.52 **<0.001**	.52 **<0.001**		.14 0.330	.15 0.274	.33 **0.016**	.39 **0.003**	.20 0.155	-.04 0.798
Total duration in prison	r p	.56 **<0.001**	-.06 0.682	.14 0.330		.59 **<0.001**	.64 **<0.001**	.71 **<0.001**	-.15 0.286	-.18 0.215
Number of CD symptoms	r p	.55 **<0.001**	-.01 0.963	.15 0.274	.59 **<0.001**		.73 **<0.001**	.65 **<0.001**	-.10 0.463	-.22 0.118
Number of ASPD symptoms	r p	.59 **<0.001**	.02 0.901	.33 **0.016**	.64 **<0.001**	.73 **<0.001**		.59 **<0.001**	.06 0.661	-.31 **0.031**
PCL:SV score	r p	.68 **<0.001**	.01 0.966	.39 **0.003**	.71 **<0.001**	.65 **<0.001**	.59 **<0.001**		.15 0.275	-.24 0.094
Total PANSS score	r p	-.08 0.555	.17 0.224	.20 0.155	-.15 0.286	-.10 0.463	.06 0.661	.15 0.275		-.16 0.269
FSIQ	r p	-.15 0.304	-.07 0.623	-.04 0.798	-.18 0.215	-.22 0.118	-.31 **0.031**	-.24 0.094	-.16 0.269	

Abbreviations: GRVS = Gunn Robertson Violence Scale; CD = conduct disorder; ASPD = antisocial personality disorder; PCL:SV = Psychopathy Checklist Screening Version; PANSS = Positive And Negative Syndrome Scale; FSIQ = Full Scale Intelligence Quotient

5.6.4 Group comparisons of clinical characteristics

The ages of the participants did not differ significantly between the groups but differences in key clinical characteristics were statistically significant (table 5-2). Three patients and none of the controls met the PCL:SV threshold indicating psychopathy. Six of the controls (15%) had a lifetime history of alcohol abuse and 1 had prior alcohol dependence. Only three controls met criteria for prior cannabis abuse and six controls for lifetime cannabis dependence. In terms of drugs other than cannabis, one control had prior cocaine abuse but there were no other instances of drug abuse or dependence among the controls. Substance use disorders among the patients are shown in table 5-3.

Table 5-2 Group differences for key clinical characteristics

Variable	**Patients n=54**	**Controls n=39**	**Test statistic**	**Significance (p value)**
Age (years)	36.06 (9.54)	32.56 (9.25)	t = -1.76	0.08
Age left full time education (years)	16.07 (2.10)	18.38 (2.15)	t = 5.19	**<0.001**
WAIS-III Full Scale Intelligence Quotient	87.94 (12.37)	108.38 (15.78)	t = 6.86	**<0.001**
Alcohol use disorder (n)	36	7	X^2 = 21.62 (df=1)	**<0.001**
Drug use disorder (n)	38	9	X^2 = 20.26 (df=1)	**<0.001**
Conduct disorder (n)	24	5	X^2 = 10.55 (df=1)	**0.001**
Antisocial personality disorder (n)	21	0	X^2 = 19.59 (df=1)	**<0.001**
Psychopathy Checklist Screening Version score	6.91 (5.22)	0.23 (0.74)	t = -7.91	**<0.001**

Data represents mean and (standard deviation) unless otherwise stated

Table 5-3 Patients' illness descriptors

Age of onset of schizophrenia (years)	22.69 (4.91)
Time since onset of schizophrenia (years)	13.39 (7.85)
Number of hospital admissions	4.24 (5.41)
Total duration in hospital (years)	6.06 (6.57)
Positive And Negative Syndrome Scale	
P score	18.26 (6.67)
N score	16.91 (4.61)
G score	33.78 (6.62)
Total score	68.94 (14.14)
Current dose of antipsychotic in chlorpromazine equivalent (mg)	544.4 (427.86)
Current location (n)	
Community	15 (28%)
Open/locked ward	19 (35%)
Low secure unit	11 (20%)
Medium secure unit	9 (17%)
Mental Health Act status (n)	
Informal	5 (9%)
Community treatment order	9 (17%)
Civil section	13 (24%)
Forensic section	27 (50%)
Conduct disorder (n)	24 (44%)
Antisocial personality disorder (n)	21 (39%)
Psychopathy Checklist Screening Version score	6.91 (5.22)
Substance use disorders (n)	
Alcohol abuse	23 (43%)
Alcohol dependence	13 (24%)
Cannabis abuse	8 (15%)
Cannabis dependence	30 (56%)

Cocaine abuse	12 (22%)
Cocaine dependence	9 (17%)
Stimulant abuse	7 (13%)
Stimulant dependence	7 (13%)
Opioid abuse	3 (6%)
Opioid dependence	9 (17%)

Data reflects mean and (standard deviation) unless otherwise stated

5.6.4.1 Clinical characteristics of patients

Patients' clinical characteristics are described in table 5-3. All in-patients were detained under the Mental Health Act and nearly two thirds of the patients living in the community were subject to a Community Treatment Order. Two patients had never been admitted to hospital. Of the fifty-four patients, seventeen were prescribed an antidepressant and nineteen a mood stabilizer. One informal patient was not taking antipsychotics as suggested by his psychiatrist but all other patients were on antipsychotic medication. Thirty-one patients (57%) were taking clozapine and could be considered clinically treatment resistant, but only eighteen (33%) had the compromised functioning and persistent psychotic symptoms necessary to meet the modified Kane criteria for treatment resistance (described in chapter 4). Sixteen patients (30%) met criteria for remission (as outlined in chapter 4).

5.6.4.2 Criminal convictions

Forty of the fifty-four patients had a criminal conviction, thirty-one for more minor violence (e.g. common assault) and twenty-three for major violence (e.g. grievous bodily harm). One patient had been convicted of murder, two of manslaughter and two of attempted murder. Five patients had been convicted of common assault but another six reported committing assaults for which they were not charged. Thirty-two patients had spent time in prison, with a mean of four periods in custody each and a mean duration in custody of twenty-two months, with a range between 0 and 12 years.

Among the controls there were relatively few instances of violence, with the most frequent incidents being common assault. Only one of the controls had a criminal conviction, which was for common assault and did not incur a custodial sentence.

5.6.5 Group comparison of behaviours from the MacArthur Community Violence Instrument

The patients had an increased lifetime frequency of all the types of aggressive behaviours compared to the controls, apart from pushing, grabbing or shoving (see table 5-4). However, choking and slapping were no longer statistically significant after adjusting for multiple comparisons.

Table 5-4 Comparison of behaviours from the MacArthur Community Violence Instrument (MCVI) between patients and controls

Behaviour from MCVI	**Mean lifetime frequency score** [a]		**Test statistic**	**Significance (p)**	
	Controls (n=39)	**Patients (n=54)**	**(U)**	**Unadjusted**	**Adjusted**
Thrown something at anyone	1.18 (sd 1.49)	2.06 (sd 1.68)	1379.5	**0.009**	**0.036**
Pushed, grabbed, or shoved	2.49 (sd 1.54)	2.91 (sd 1.85)	1221.5	0.181	0.181
Slapped	0.77 (sd 1.31)	1.50 (sd 1.75)	1299.5	**0.036**	0.084
Kicked	1.21 (sd 1.30)	2.22 (sd 1.65)	1431.0	**0.002**	**0.010**
Bitten	0.05 (sd 0.32)	0.46 (sd 0.84)	1334.5	**0.001**	**0.006**
Choked	0.23 (sd 0.74)	0.48 (sd 0.82)	1247.5	**0.042**	0.084
Hit anyone with a fist or object	1.69 (sd 1.44)	3.31 (sd 1.44)	1647.5	**<0.001**	**0.006**
Threatened anyone with a weapon	0.13 (sd 0.47)	1.56 (sd 1.42)	1710.0	**<0.001**	**0.006**

Used a weapon	0.05 (sd 0.22)	1.26 (sd 1.40)	1623.5	**<0.001**	**0.006**

a) Based on the 0-5 frequency scale of the Life History of Aggression (see 4.7.1 in chapter 4)

5.6.6 Group comparison of Gunn Robertson Violence Scale ratings

The distribution of Gunn Robertson Violence Scale ratings for both groups is shown in figure 5-1. The mean Gunn Robertson Scale rating for the patients was 2.41 and for the controls was 0.59 ($U=1835.5$, $p<0.001$), demonstrating that the patients had a greater lifetime propensity to violence than the healthy controls.

5.6.7 Validity of the Gunn Robertson Violence Scale as a measure of lifetime propensity to violence

5.6.7.1 Construct validity

Associations between the GRVS and other constructs with well-established associations with violence were analysed (table 5-5). Due to the low levels of violence and conduct disorder in the control group, these analyses were restricted to the patient group. Due to the low rate of psychopathy, PCL:SV score rather than the presence of psychopathy, was used in these analyses.

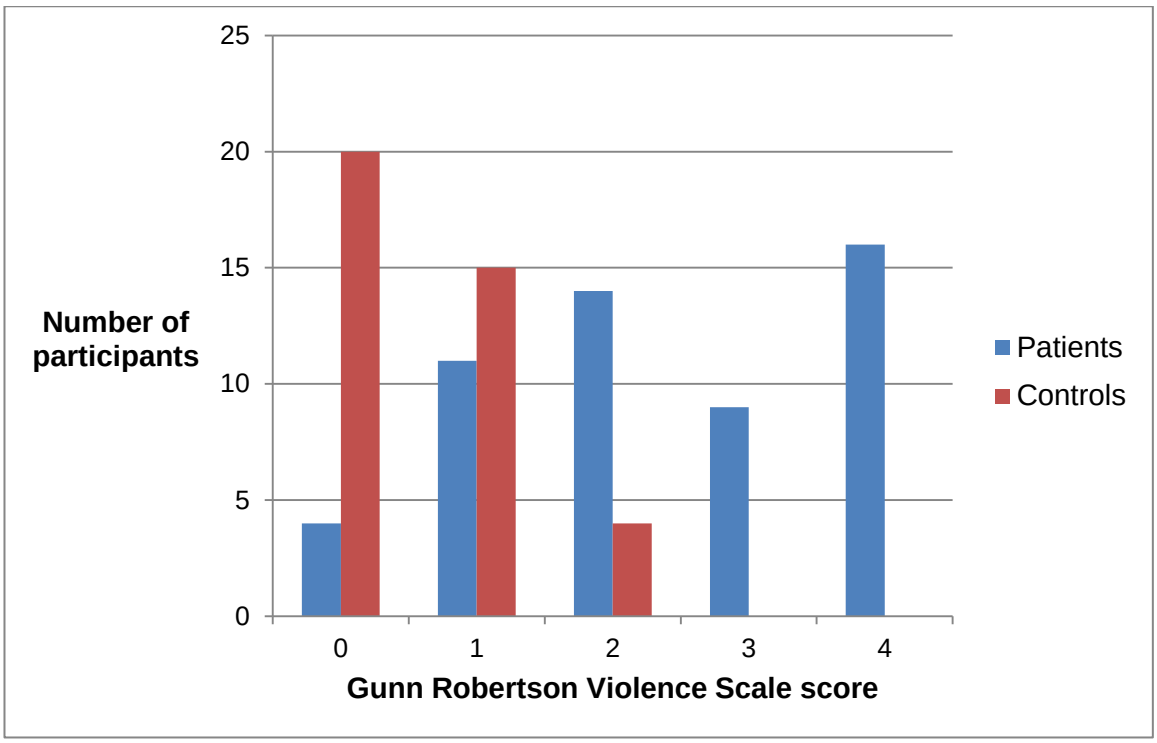

Figure 5-1 Gunn Robertson Violence Scale (GRVS) ratings in patients and controls

Table 5-5 Associations between GRVS and established variables associated with violence

Variable	Odds ratio	95% CI	Test statistic (Wald X^2)	Standard error	Significance (p)	
					Unadjusted	Adjusted
Antisocial personality disorder	9.77	3.10, 30.78	15.12	0.59	**<0.001**	**0.002**
Conduct disorder	9.87	3.19, 30.61	15.74	0.58	**<0.001**	**0.002**
PCL:SV score	1.45	1.22, 1.68	25.51	0.07	**<0.001**	**0.002**
Substance use disorders	24.75	5.16, 118.85	16.08	0.80	**<0.001**	**0.002**
Total duration in prison (months)	1.03	1.01, 1.05	10.84	0.01	**0.001**	**0.002**

5.6.7.2 Concurrent validity

5.6.7.2.1 Severity of violence

GRVS scores were compared with the categories used in studies utilizing the MCVI and this cross-tabulation is shown in table 5-6. All GRVS scores of 4, and all but one scores of 3, would be categorised as violence. GRVS scores of 1 and 2 were split between the categories of violence and other aggressive acts.

Table 5-6 Comparison of GRVS scores with violence categories used in the MacArthur Violence Risk Assessment Study (1998)

Gunn Robertson Violence Scale	**No violence**	**Other aggressive acts**	**Violence**	**Total**
0	2	2	0	4
1	0	7	4	11
2	0	4	10	14
3	0	1	8	9
4	0	0	16	16

5.6.7.2.2 Frequency of violence

The above considers the severity of the violence, in order to try to assess the validity of the GRVS in relation to capturing frequency of violence, it was compared with frequency of one of the aggressive behaviours in the MCVI (use of a weapon was selected as this would capture the most severe forms of violent behaviour). This is shown in table 5-7, which indicates that increasing GRVS scores have an increasing frequency of use of a weapon.

Table 5-7 Comparison of frequency scores for lifetime use of a weapon with GRVS scores

Scale		Frequency scores for use of a weapon [a]						
		0	**1**	**2**	**3**	**4**	**5**	**Total**
Gunn Robertson Violence Scale	**0**	24	0	0	0	0	0	24
	1	24	2	0	0	0	0	26
	2	10	4	3	1	0	0	18
	3	1	3	0	5	0	2	9
	4	1	4	5	3	1	2	16
	Total	60	13	8	9	1	2	93

a) Based on the 0-5 frequency scale of the Life History of Aggression (see 4.7.1 in chapter 4)

5.6.8 Conduct disorder, antisocial personality disorder and psychopathy and violence

These analyses were conducted in the patients only due to the low levels of CD, ASPD and psychopathy in the healthy controls. Twenty-four patients were diagnosed with prior CD, twenty-one with ASPD and three had a PCL:SV score indicating psychopathy. After adjusting for substance use disorders, CD and ASPD were significantly associated with an increased GRVS score and the presence of each symptom of CD and ASPD was also associated with an increased propensity to violence (see table 5-8). The PCL:SV score was also associated with violence.

Table 5-8 Associations between GRVS and conduct disorder, antisocial personality disorder and psychopathy

Variable	Adjusted Odds Ratio [a]	95% CI	Test statistic (Wald X^2)	Standard error	Significance (p)	
					Unadjusted	Adjusted
CD	5.24	1.61, 17.04	7.59	0.60	**0.006**	**0.006**
CD symptoms	1.32	1.09, 1.60	8.08	0.10	**0.004**	**0.006**
ASPD	5.57	1.70, 18.19	8.10	0.60	**0.004**	**0.006**
ASPD symptoms	1.87	1.31, 2.66	12.09	0.18	**0.001**	**0.004**
PCL:SV score	1.37	1.18, 1.58	17.59	0.07	**<0.001**	**0.004**

a) Adjusted for the lifetime presence of a substance use disorder

Abbreviations: CD = conduct disorder; ASPD = antisocial personality disorder; PCL:SV = Psychopathy Checklist Screening Version

In terms of CD specifically, those with prior CD had more frequently engaged in all behaviours assessed by the MCVI, apart from choking, as shown in table 5-9. These associations remained statistically significant after adjusting for multiple testing.

Table 5-9 Comparisons of behaviours from the MacArthur Community Violence Instrument (MCVI) in patients with and without prior conduct disorder

Behaviour from MCVI	Mean lifetime frequency score [a]		Test statistic (U)	Significance (p)	
	Conduct disorder (n=24)	No conduct disorder (n=30)		Unadjusted	Adjusted
Thrown something at anyone	2.75 (sd 1.75)	1.50 (sd 1.41)	213.0	**0.009**	**0.018**
Pushed, grabbed, or shoved	3.79 (sd 1.74)	2.20 (sd 1.63)	171.0	**0.001**	**0.004**

Slapped	2.38 (sd 2.00)	0.80 (sd 1.13)	195.5	**0.002**	**0.006**
Kicked	3.08 (sd 1.56)	1.53 (sd 1.38)	173.0	**0.001**	**0.004**
Bitten	0.92 (sd 1.06)	0.10 (sd 0.31)	192.0	**<0.001**	**0.004**
Choked	0.63 (sd 0.97)	0.37 (sd 0.67)	315.5	0.344	0.344
Hit anyone with a fist or object	4.08 (sd 1.02)	2.70 (sd 1.44)	161.5	**<0.001**	**0.004**
Threatened anyone with a weapon	2.42 (sd 1.38)	0.87 (sd 1.04)	138.5	**<0.001**	**0.004**
Used a weapon	2.21 (sd 1.38)	0.50 (sd 0.86)	110.5	**<0.001**	**0.004**

a) Based on the 0-5 frequency scale of the Life History of Aggression (see 4.7.1 in chapter 4)

5.6.9 Aggressive attitudes

5.6.9.1 All participants

Higher total score on the Buss Perry Aggression Questionnaire (BPAQ) was associated with an increased propensity to violence (p=0.004) after controlling for substance use disorders, but this did not remain statistically significant after adjusting for psychopathy. Therefore aggressive attitudes were not associated with an increased lifetime propensity to violence. When considering the sub-scales of the BPAQ, verbal aggression and anger were not associated with propensity to violence after adjusting for substance use disorders. The hostility (p=0.04) and physical aggression (p<0.001) sub-scales were associated with violence after adjusting for substance use disorders but did not remain statistically significant after also adjusting for psychopathy.

5.6.9.2 Patients only

On univariate analysis, higher total score on the BPAQ was associated with an increased propensity to violence (p=0.037) but this did not remain statistically significant after adjustments. In terms of the sub-scales of the BPAQ, both verbal aggression (p=0.025) and physical aggression (p=0.005) were associated with violence on univariate analyses but did not remain statistically significant after adjustments. Anger and hostility sub-scales were not associated with violence.

Prior CD was associated with increased aggressive attitudes in adulthood; total and sub-scale scores on the BPAQ in patients with, and without, prior conduct disorder (table 5-10). The hostility sub-scale of the BPAQ is correlated with the P and G symptom scales and total score on the PANSS (table 5-11).

Table 5-10 Comparisons of Buss Perry Aggression Questionnaire scores in patients with and without prior conduct disorder

Buss Perry Aggression Questionnaire	**Mean score**		**Test statistic (U)**	**Significance (p)**	
	Conduct disorder (n=24)	**No conduct disorder (n=30)**		**Unadjusted**	**Adjusted**
Total score	95.00 (sd 24.01)	71.93 (sd 19.24)	162.5	**0.001**	**0.003**
Physical aggression sub-scale	31.92 (sd 8.52)	21.27 (sd 8.18)	143.0	**<0.001**	**0.003**
Verbal aggression sub-scale	16.83 (sd 4.98)	12.20 (sd 4.41)	173.5	**0.001**	**0.003**
Anger sub-scale	20.83 (sd 7.15)	15.33 (sd 4.68)	188.0	**0.003**	**0.006**
Hostility sub-scale	25.42 (sd 8.10)	23.13 (sd 6.87)	302.5	0.316	0.316

Table 5-11 Correlations between PANSS and BPAQ among patients (n=54)

	Correlation	P total	N total	G total	PANSS total score	BP physical aggression	BP verbal aggression	BP anger	BP hostility	BP total score
P total	r p		.22 0.119	.49 **<0.001**	.82 **<0.001**	.40 **0.003**	.15 0.281	.41 **0.002**	.53 **<0.001**	.48 **<0.001**
N total	r p	.22 0.119		.49 **<0.001**	.59 **<0.001**	.01 0.920	-.02 0.873	.02 0.873	.24 0.080	.07 0.597
G total	r p	.49 **<0.001**	.49 **<0.001**		.93 **<0.001**	.20 0.152	.10 0.480	.11 0.411	.38 **0.004**	.26 0.058
PANSS total score	r p	.82 **<0.001**	.59 **<0.001**	.93 **<0.001**		.26 0.056	.10 0.468	.22 0.105	.47 **<0.001**	.34 **0.011**
BP physical aggression	r p	.40 **0.003**	.01 0.920	.20 0.152	.26 0.056		.71 **<0.001**	.65 **<0.001**	.48 **<0.001**	.91 **<0.001**
BP verbal aggression	r p	.15 0.281	-.02 0.873	.10 0.480	.10 0.468	.71 **<0.001**		.58 **<0.001**	.36 **0.007**	.75 **<0.001**
BP anger	r p	.41 **0.002**	.02 0.873	.11 0.411	.22 0.105	.65 **<0.001**	.58 **<0.001**		.53 **<0.001**	.81 **<0.001**
BP hostility	r p	.53 **<0.001**	.24 0.080	.38 **0.004**	.47 **<0.001**	.48 **<0.001**	.36 **0.007**	.53 **<0.001**		.71 **<0.001**
BP total score	r p	.48 **<0.001**	.07 0.597	.26 0.058	.34 **0.011**	.91 **<0.001**	.75 **<0.001**	.81 **<0.001**	.71 **<0.001**	

Abbreviations: PANSS = Positive And Negative Syndrome Scale (sub-scales for Positive symptoms, Negative symptoms and General psychopathology); BPAQ = Buss Perry Aggression Questionnaire (sub-scales for physical aggression, verbal aggression, anger and hostility)

5.6.10 Instrumental violence

For seven of the fifty-four patients (13%), their most serious act of violence during their adult life was instrumental in nature. Six of these seven patients had pre-morbid CD and the patient without CD was the only one who did not have a GRVS score of 4. The seven included all three patients in the sample who met the threshold indicating psychopathy (all three of whom had a GRVS score of 4). The mean PCL:SV score of these seven patients with instrumental violence was 13.7 and the rest of the patients was 5.9 ($t=4.25$, $p<0.001$).

5.7 Discussion

This study has demonstrated that the GRVS has good inter-rater reliability, good construct validity and reasonable concurrent validity. CD, ASPD and PCL:SV score are all associated with GRVS after controlling for substance use disorders. Those patients with pre-morbid CD more frequently engaged in all violent behaviours assessed, apart from choking, indicating CD is a significant factor influencing later propensity to violence. Aggressive attitudes measured by the BPAQ, were not associated with violence after relevant adjustments, either in all participants or the patient group only. However, pre-morbid CD was associated with aggressive attitudes in adulthood, apart from the hostility sub-scale which was associated with current psychotic symptoms. Instrumental violence was associated with a higher psychopathy score.

5.7.1 Validity of the Gunn Robertson Violence Scale as a measure of lifetime propensity to violence

The original paper describing the development of the Gunn Robertson Scale within a prison population (Gunn and Robertson, 1976), reported very good inter-rater reliability while the authors acknowledged the difficulties of assessing its validity. In this study we also achieved good inter-rater reliability for the violence sub-scale of the Gunn Robertson Scale in a population of men with schizophrenia in a variety of mental health settings and healthy controls. Concurrent validity was considered by comparing the GRVS scores with the MCVI data, and construct validity by assessing associations between the GRVS and factors known to be linked to violence. A modest degree of concurrent validity was found for both severity and frequency of violent behaviours. Good construct validity was suggested by the significant associations

between the GRVS and other factors associated with the risk of violence, namely CD, ASPD, psychopathy and substance use disorders.

This data suggests the GRVS has reasonable validity in this population. The GRVS offers significant advantages over the practice of dichotomising subjects as violent or non-violent on the basis of an arbitrary threshold and it incorporates some indices of severity, frequency and outcome of the violence. Therefore, we conclude that the GRVS is a good means of quantifying lifetime violence propensity amongst men with schizophrenia.

The question in the MCVI 'Have you kicked, bitten, or choked anyone?' was disaggregated (see chapter 4) into the three separate behaviours (Michie and Cooke, 2006). Choking and biting were relatively rare in this sample, both among patients and controls, while kicking was much more common. Choking was the only behaviour which did not differ between patients with, and without, prior CD, although this could be a reflection of lack of power due to the low numbers who engaged in the behaviour. The differences in the frequencies of these three behaviours would seem to support the benefit of disaggregating the question, potentially allowing the collection of richer information about seemingly different behaviours.

Using the MCVI to score the GRVS reduces the detail available from the data but is an improvement in the quantification of violence compared to earlier studies which employed the MCVI but then classified participants only into 'violent' or 'other aggressive acts' categories (Steadman et al., 1998, Appelbaum et al., 2000, Swanson et al., 2006), as with the GRVS there are five categories of violence. Michie and Cooke (2006) suggested a hierarchy of severity of behaviours in the MCVI, which could allow consideration of the individual MCVI behaviours as a more detailed overall measure of violence. However, this approach is limited by the consequent need for a very large sample size, to give enough data for each individual aggressive behaviour, to allow meaningful statistical analyses. Use of the GRVS may be more pragmatic but there is scope for further development of the scale. For example, the GRVS score of 3 is based on number of convictions only and it would be preferable to also include an element of self-report like the other scores on the scale (Harris et al., 2013). It would also be beneficial to research the use of the scale in people with other mental disorders.

5.7.2 Conduct disorder, antisocial personality disorder, psychopathy and violence

In this sample of men with schizophrenia, 44% had prior CD, a finding strikingly consistent with previous studies of those with severe mental illness (Hodgins et al., 2008, Kim-Cohen et al., 2003). It has been suggested that longitudinal, prospective studies are needed to understand why CD is more common among people with schizophrenia (Hodgins et al., 2008). Both schizophrenia (Murray and Lewis, 1988) and CD (Blair et al., 2014) are neurodevelopmental disorders, where a combination of genetic and environmental factors interact to modify the normal trajectory of brain development and behaviour. From an aetiological perspective one possible explanation for why CD is more common among people with schizophrenia than the general population, is that a proportion of genetic and environmental factors that influence the risk of developing each disorder are common between them. For example, there is evidence that childhood physical abuse is more common in those who develop schizophrenia (Rosenberg et al., 2007) and is also more common among those with a history of CD (Afifi et al., 2011), leading to the hypothesis that physical abuse is important in the aetiology of both (Hodgins et al., 2008).

Patients with prior CD, and those who went on to have ASPD, had an increased lifetime propensity to violence, compared to patients without prior CD. This association was present at the level of the individual symptoms of these disorders, as it was for the PCL:SV score. This finding highlights that even a few symptoms of CD in childhood or adolescence is associated with an increased likelihood of aggressive behaviour in adulthood. This is in line with a previous study of men and women with severe mental illness (Hodgins et al., 2008) and one of men with schizophrenia or schizoaffective disorder (Hodgins et al., 2005), where the number of CD symptoms present prior to the age of 15 significantly increased the risk of violent crime after controlling for alcohol and illicit drug use.

These results are relevant to clinical practice, showing it is important to carefully consider symptoms of CD, ASPD and psychopathy, even if full diagnostic criteria are not met, in order to inform a risk assessment. As special training is required to administer the PCL:SV, the association with the number of CD symptoms is important, as these can potentially be assessed

more easily. Patients with prior CD can be easily identified at first presentation to mental health services by conducting the relevant interview, allowing them to be identified as a high risk group for behaving violently. This would allow a structured package of interventions to be offered to address their aggressive behaviour, any co-morbid substance misuse and other relevant psychosocial deficits, with the aim of reducing the risk of violence. Ideally, early intervention in childhood could reduce the risk of violence in adulthood. Children with CD would be an important group to target in terms of violence prevention and there are effective treatments available for CD, particularly parenting training (Weisz et al., 2004, Scott, 2008).

5.7.3 Aggressive attitudes

The physical aggression, verbal aggression and anger sub-scales and total score on the BPAQ were all significantly higher in patients with prior CD. This association with CD may contribute to the explanation of why BPAQ was no longer associated with propensity for violence after controlling for psychopathy. A potential explanation for the lack of increased scores on the hostility sub-scale among those with CD is its correlation with the PANSS scores, suggesting the hostility score is associated with current psychotic symptoms. It can certainly be seen that some items in the BPAQ could be descriptive of paranoid ideation, for example, '*I sometimes feel that people are laughing at me behind my back'* (Buss and Perry, 1992).

Anger has consistently been shown to be associated with violence in the general population (Anderson and Bushman, 2002). Whilst the current study did not support this, there is evidence that trait anger is associated with violence in schizophrenia (Reagu et al., 2013, Nederlof et al., 2011). However, an area of emerging importance in the literature, is the role of anger in response to psychotic symptoms as a possible mediator or correlate of the relationship between aggressive behaviour and psychotic symptoms in schizophrenia (Coid et al., 2013, Ullrich et al., 2014, Bucci et al., 2013, Reagu et al., 2013). The interplay of trait anger, and state anger in response to psychotic symptoms, would be an interesting focus for future research in the field.

5.7.4 Instrumental violence

There was a relatively low level of instrumental violence in this sample of men with schizophrenia. This fits with only three patients meeting the threshold indicating psychopathy. All three of these patients used instrumental violence and had a GRVS score of 4 indicating the seriousness of the violence they had perpetrated. As hypothesized, instrumental violence was associated with a higher PCL-SV score. This is in keeping with the literature suggesting co-morbid psychopathy is associated with a significantly increased risk of violence in schizophrenia (McGregor et al., 2012, Tengström et al., 2000, Tengström et al., 2004, Bo et al., 2011).

5.8 Strengths and limitations

5.8.1 Strengths

The sample is well-defined and described, containing a range of both in-patients and out-patients with varying levels of symptomatology and a range of histories of violence. The participants underwent a comprehensive assessment of both their background history (generally and in relation to violence) and their mental disorders. The use of the GRVS has allowed a more careful quantification of violence.

5.8.2 Limitations

As described in 4.7.5.2, it was not possible to obtain the Police National Computer records for study participants. This meant that there was no method of confirming the details of convictions or cautions reported by participants or their family members. For patient participants, their medical records were examined, which did provide further information from another source about any violent behaviour. Multiple sources of information are desirable in order to ensure high quality, accurate information regarding any violent behaviour of the individual, and the inability to obtain PNC records resulted in a reduced number of sources of information. However, self-report of violence has been shown to be reliable and valid, with patients reporting five times more violent acts than those documented in official records (Steadman et al., 1998). Therefore, it is unlikely that the lack of PNC records has led to an under-estimate of violence in the sample.

This study is limited by its cross-sectional design, which does not allow temporal proximity between the measurement of the clinical variables and the violent behaviour. A prospective methodology would allow this type of analyses but would require a very large sample and a long follow-up period due to the relative rarity of incidents of severe violence. However, this chapter has considered the presence of relatively stable disorders (CD, ASPD, psychopathy) and the lifetime propensity to violence, so temporal proximity is less crucial. It was not possible to test the contribution of CD only to lifetime propensity to violence, compared to CD progressing to ASPD, as there were only three patients in the sample with CD only. This would be a useful focus for future research.

In addition, none of the healthy controls in this study had a significant history of violence and this meant that analyses relating to violence were limited to the patient group. It was not possible to compare violent participants with and without schizophrenia; in order to achieve this in future studies, it would be necessary to actively recruit control participants from criminal justice settings such as probation offices and prisons.

5.9 Conclusions

The GRVS is a useful method of quantifying violence in men with schizophrenia and appears to have good inter-rater reliability and validity. CD prior to the age of 15 is important in determining the lifetime propensity for violence in men with schizophrenia. This association is present at the level of individual CD symptoms and indicates that it would be useful to carefully assess these symptoms among patients presenting with schizophrenia to inform their risk assessment and management.

Chapter 6 Childhood adversity and conduct disorder

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6.1 Introduction to published paper

This paper examines the association between childhood adversity and propensity to violence in adulthood among men with schizophrenia. The literature which informed the generation of the hypotheses described in this paper was outlined in section 2.6. In summary, there is emerging evidence that childhood adversity, perhaps acting at critical periods of childhood development, is associated with conduct disorder, psychosis, and the risk of violence. The methodology is described within the published paper and follows the same general methodology of the rest of this research, as described in chapter 4.

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Childhood adversity and conduct disorder: A developmental pathway to violence in schizophrenia

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ABSTRACT

Background: Both childhood adversity and conduct disorder are over-represented among adult patients with schizophrenia and have been proposed as significant factors that may increase the risk of violence. It is not known how childhood adversity and conduct disorder might interact to contribute towards an increased risk of violence in schizophrenia. This study aimed to explore the relationships between childhood adversity, conduct disorder and violence among men with schizophrenia.
Methods: 54 male patients with schizophrenia from a range of inpatient and outpatient mental health services were assessed for exposure to a variety of childhood adversities, conduct disorder before the age of 15 and later violent behaviour in adulthood.
Results: Exposure to domestic violence during childhood was associated with an increased propensity to violence in adulthood. Symptoms of conduct disorder were associated both with cumulative exposure to childhood adversities and with later propensity to violence. The cumulative number of childhood adversities was associated with adult propensity to violence. This association was significantly attenuated by inclusion of conduct disorder in the model.
Conclusions: This is the first study to demonstrate an association between childhood exposure to domestic violence and later violent behaviour in schizophrenia. Conduct disorder may mediate the association between cumulative childhood adversities and adult propensity to violence, indicating an indirect pathway. These results indicate a complex interplay between childhood adversity, conduct disorder and later violent behaviour in schizophrenia, and suggest that there may be shared aetiological risk factors on a common developmental pathway to violence.

1. Introduction

There is good epidemiological evidence to support a modest but significant association between schizophrenia and violence (Arseneault et al., 2000; Douglas et al., 2009; Large and Nielssen, 2011; Walsh et al., 2002) but the origins of this relationship remain unclear. Some argue that little violence risk is attributable to the mental illness itself, with the effects of substance abuse (particularly alcohol) and personality disorders outweighing the role of schizophrenia (Appelbaum, 2008).

It is established that co-morbid substance misuse increases the risk of violence in schizophrenia (Elbogen and Johnson, 2009; Fazel et al., 2009; Swanson et al., 2006). Controversy remains about the true extent of that role. Some studies have cited substance misuse as one of several factors that increase the risk of violent behaviour in patients with psychotic illnesses (Daffern et al., 2005; Dean et al., 2007; Harris et al., 2010; Stompe et al., 2004). Other large epidemiological studies have suggested that there is almost no role for psychosis-specific factors and that substance misuse is the main driver of violence in schizophrenia (Elbogen and Johnson, 2009; Fazel et al., 2009). However a reanalysis of the data from one of these (Elbogen and Johnson, 2009) found that those patients with severe mental illness, irrespective of substance abuse comorbidity, were significantly more likely to be violent than those with no mental illness (Van Dorn et al., 2012). Equally there is data that patients with schizophrenia without comorbid substance misuse, do have an elevated risk of violence (Short et al., 2013).

Antisocial personality disorder increases the risk for violence in men with schizophrenia (Volavka, 2014). In some patients with schizophrenia, personality pathology, including psychopathy, predicts violence regardless of schizophrenia symptoms (Bo et al., 2011). Taken together these findings have led to the suggestion that violence among patients with schizophrenia may follow at least two distinct pathways, one associated with premorbid conditions, including antisocial behaviour, and another linked with the acute psychotic symptoms of schizophrenia (Bo et al., 2011; Hodgins et al., 2014; Volavka, 2014; Volavka and Citrome, 2011).

Threat/control-override symptoms, principally delusions of persecution and passivity were advanced as a cognitive model for violence in psychosis (Link and Stueve, 1994). Though supporting evidence has remained limited (Appelbaum et al., 2000; Stompe et al., 2004). Other

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studies have concluded that positive psychotic symptoms do increase the risk of violence (Daffern et al., 2005; Hodgins et al., 2003; Krakowski et al., 1999; Swanson et al., 2006). Crucially there are early indicators that psychotic symptoms may be of particular relevance in relation to violence committed by patients with schizophrenia in the absence of preceding conduct disorder (Heads et al., 1997; Swanson et al., 2008).

Childhood physical abuse has been shown to be associated with later violent behaviour in general population (Elbogen and Johnson, 2009), patient (Hoptman et al., 1999; Witt et al., 2013) and prisoner (Sarchiapone et al., 2009) samples. However, less is known about the influence of other forms of childhood trauma on the risk of violence in people with schizophrenia.

Childhood adversity is strongly associated with an increased risk for psychosis and could have a significant aetiological role (Varese et al., 2012). For example, a prospective study in adolescents showed that childhood trauma was strongly predictive of new psychotic experiences and that stopping the trauma stopped the psychotic experiences (Kelleher et al., 2013). There is also evidence that childhood abuse and number of later life events combine synergistically to increase the odds of psychotic experiences beyond the effects of each risk factor alone (Morgan et al., 2014). However, other forms of childhood adversity, such as parental loss or separation also contribute to later psychopathology (Morgan et al., 2007). Hence there is a wider focus on the effects of childhood adversities in psychosis, rather than exclusively childhood trauma (Varese et al., 2012).

One important influence on the later effects of childhood adversity may be conduct disorder. Childhood abuse is associated with a wide range of later psychopathology (McCrory et al., 2012). Childhood adversity, including neglect and physical and sexual abuse, increases the risk of conduct disorder (Afifi et al., 2011; Foley et al., 2004; Maniglio, 2015; Villodas et al., 2014); while conduct disorder (CD) is over-represented in patients who later develop schizophrenia (Hodgins et al., 2008). Finally childhood CD is associated with an increased risk of violent behaviour in both the adult general population (Blair et al., 2014) and in those with schizophrenia (Arseneault et al., 2000; Hodgins et al., 2008; Swanson et al., 2008; Tengström et al., 2004).

In summary, there is emerging evidence that childhood adversity is associated with psychosis, CD and the risk of violence. However, it remains unclear how childhood adversity might interact with CD to contribute towards the increased risk of violence in schizophrenia. This study, therefore, sought to examine the association between childhood adversity and violence among men with schizophrenia and whether this varied on the basis of prior CD. Patients with schizophrenia are more likely to have been exposed to a variety of adverse childhood events including physical and sexual abuse; parental divorce, parental death; domestic violence; and foster care (Bennouna-Greene et al., 2011; Gibbon et al., 2009; Rosenberg et al., 2007). Therefore this study considered three types of childhood adversity: childhood abuse (physical or sexual); separation from either parent (due to reasons such as divorce, death, or being taken into foster care); and exposure to domestic violence. We hypothesised that among men with schizophrenia, those with prior CD would be more likely to (i) report childhood adversities and (ii) have a significantly greater history of violence, as compared to those without CD. We further hypothesised that childhood adversities would be associated with violence and that CD would be a mediator of the relationship between childhood adversities and violence.

2. Methods

2.1. Recruitment

After NHS Research Ethics Committee approval, male patients of working age with schizophrenia were recruited from four large National Health Service Mental Health Trusts and one independent sector provider. The sites had a range of mental health services for men with schizophrenia, including outpatient clinics and inpatient wards in acute as well as secure units. This approach offered representative sampling of male patients with schizophrenia in their respective catchment areas, across a wide geographical region of England, encompassing socially and ethnically diverse populations. Potential candidates were identified and referred by their consultant psychiatrist. Participants were excluded if they had a history of: epilepsy, significant head injury, learning/intellectual disability or dementia, neurological disorder, mania or hypomania or current active substance abuse/dependence. All participants gave their written informed consent after a full description of the study aims and procedures.

2.2. Clinical assessment

Diagnoses of schizophrenia and lifetime substance use disorders were established using the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 2002). Psychotic symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Current antipsychotic load was calculated from the patients' prescription (Gardner et al., 2010). CD and antisocial personality disorder (ASPD) were assessed using the Structured Clinical Interview for DSM-IV Axis II disorders (SCID-II) (First et al., 1997). The Psychopathy Checklist Screening Version (PCL:SV) (Hart et al., 1995) was also rated, which is a screening tool for psychopathy which is robustly related to the full Psychopathy Checklist Revised (PCL-R) (Guy and Douglas, 2006).

The Childhood Experiences of Care and Abuse Questionnaire (CECA-Q) (Bifulco et al., 2005) assesses retrospective reports of childhood maltreatment and is reliable in people with psychotic disorders (Fisher et al., 2011). A modified version of the CECA-Q was employed (Hepgul et al., 2012), in which the interview was also augmented to ask participants about exposure to domestic violence between parental figures or family members in their childhood home. In light of the experimental hypotheses, the analyses focused on the presence of the following three types of childhood adversity before the age of 17: childhood abuse, which was dichotomized to indicate the presence of physical or sexual abuse or both; separation from either parent for 6 months or more; and exposure to domestic violence.

2.3. Assessment of violence

All participants were asked about their history of violent behaviour based on the MacArthur Community Violence Instrument (Steadman et al., 1998). Participants indicated how many times over their adult lifetime they had engaged in each type of aggressive behaviour. Self-report using this instrument is reliable and valid, in the original study patients reported 5 times more violent acts than those documented in official records (Steadman et al., 1998). Collateral information was obtained from medical records for all participants and family informants where available. Participants were also asked about any contact with the police and criminal justice system.

We sought to capture each participant's lifetime propensity to violence and based on our review (Harris et al., 2013), we selected the Gunn–Robertson Scale, which rates nine different types of offending behaviours (including violence) on a five point scale (Gunn and Robertson, 1976). The Gunn–Robertson Violence Scale (GRVS) incorporates data on several facets of violence including frequency, severity, victim injury and legal consequences. Two authors (CO and SH) independently rated all participants using the GRVS and cases of disagreement were resolved after case review to reach a consensus rating.

2.4. Statistical analyses

All statistical analyses were conducted in SPSS 18. A significance level of $p < 0.05$ was adopted throughout. Chi-square was used to test for differences between groups with and without prior CD. As the GRVS is an ordinal scale, ordinal logistic regression was used to

determine whether variables were statistically significant correlates of violence. The ordinal logistic regression is based on the proportional odds model, the parameters of which represent the odds ratios of being in the highest compared to the lowest categories. Univariate associations with violence were investigated by calculating odds ratios (OR) with 95% confidence intervals (CI). Those variables which were significantly associated with violence in univariate analyses were entered into a final ordinal logistic regression model. Mediation analyses were carried out by testing the necessary triangular associations of statistically significant relationships. Substantial attenuation in the effect magnitude of the association between independent and dependent variable after co-variation of the mediator variable was interpreted as evidence of an indirect pathway (Ullrich et al., 2014).

3. Results

3.1. Sample characteristics

A total of 54 men with schizophrenia aged between 21 and 57 (mean 36) years old were recruited from the spectrum of mental health services. Thirty-four were white British, 6 white and black Caribbean, 6 black Caribbean, 5 Asian and 3 were of other ethnic backgrounds. The characteristics of the sample are shown in Table 1. Inter-rater reliability for the GRVS scores was 89.4%.

3.2. Univariate associations with violence

Age, ethnicity and current psychotic symptoms were considered as potential confounders based on the existing literature. However, in this sample, there was no association between any of them and lifetime propensity to violence (GRVS score). A lifetime history of a substance use disorder was associated with propensity to violence (OR = 24.75, CI 5.16–118.85, $p < 0.001$) and so was controlled for in all analyses by inclusion in the final regression model. CD (OR = 5.24, CI 1.61–17.04, $p = 0.006$), ASPD (OR = 5.57, CI 1.70–18.19, $p = 0.004$) and PCL:SV score (OR = 1.37, CI 1.18–1.58, $p < 0.001$) were all associated with violence. There was moderate correlation between symptoms of CD, and ASPD, and PCL:SV, suggesting a degree of co-linearity entirely consistent with their clinical constructs. Therefore, for analyses of hypotheses relating to CD, ASPD and PCL:SV were not included in final regression models due to this co-linearity. In other analyses, PCL:SV score was included in the models as it was the most strongly associated of the three variables with GRVS score.

3.3. Childhood adversity and conduct disorder

Two patients declined to answer questions about childhood abuse but answered those about exposure to domestic violence. Reported rates of child abuse, exposure to domestic violence and parental separation were not associated with current positive psychotic symptoms (P score on PANSS) ($p > 0.5$). Child abuse and separation from a parent were both significantly associated with CD ($X^2 = 6.03$, $p = 0.014$; $X^2 = 11.11$, $p = 0.001$), while there was a trend between exposure to domestic violence and CD ($X^2 = 3.01$, $p = 0.083$).

3.4. Childhood adversity and violence in adulthood

An ordinal logistic regression model was used to assess the associations between the three types of childhood adversity and propensity to violence (GRVS score) and are shown in Table 2. Exposure to domestic violence was significantly associated with lifetime propensity to violence, after adjusting for lifetime substance use disorders and psychopathy. As there was a high prevalence of child abuse (79%) and parental separation (85%) among those who reported witnessing domestic violence and in order to control for any inter-relationships between adversities, child abuse and separation from parents were then included in the model for exposure to domestic violence but had little effect on its association with propensity to violence ($p = 0.017$). Of the patients who were rated the most violent (GRVS score of 4), 94% had experienced at least one form of childhood adversity, while 31% of them reported experiencing all three forms.

Table 1
Characteristics of the sample.

Age of onset of schizophrenia (years)	22.69 (4.91)
Time since onset of schizophrenia (years)	13.39 (7.85)
Number of hospital admissions	4.24 (5.41)
Total duration in hospital (years)	6.06 (6.57)
Positive And Negative Syndrome Scale	
P score	18.26 (6.67)
N score	16.91 (4.61)
G score	33.78 (6.62)
Total score	68.94 (14.14)
Current dose of antipsychotic in chlorpromazine equivalent (mg)	544.4 (427.86)
Current location (n)	
Community	15 (28%)
Open/locked ward	19 (35%)
Low secure unit	11 (20%)
Medium secure unit	9 (17%)
Mental Health Act status (n)	
Informal	5 (9%)
Community treatment order	9 (17%)
Civil section	13 (24%)
Forensic section	27 (50%)
Conduct disorder (n)	24 (44%)
Antisocial personality disorder (n)	21 (39%)
Psychopathy Checklist Screening Version score	6.91 (5.22)
Substance use disorders (n)	
Alcohol abuse	23 (43%)
Alcohol dependence	13 (24%)
Cannabis abuse	8 (15%)
Cannabis dependence	30 (56%)
Cocaine abuse	12 (22%)
Cocaine dependence	9 (17%)
Stimulant abuse	7 (13%)
Stimulant dependence	7 (13%)
Opiate abuse	3 (6%)
Opiate dependence	9 (17%)
Gunn–Robertson Violence Scale score (n)	
0	4 (7%)
1	11 (20%)
2	14 (26%)
3	9 (17%)
4	16 (30%)
Criminal offending (n)	
No convictions	14 (26%)
Non-violent conviction (e.g. theft)	8 (15%)
Minor violence (e.g. assault)	9 (17%)
Major violence (e.g. wounding)	23 (43%)
Served a prison sentence	32 (59%)
Total duration in prison (years)	1.86 (2.88)

Data reflect mean and (standard deviation) unless otherwise stated.

Table 2
Childhood adversity and propensity to violence.

Childhood adversity	OR	95% CI	p	AOR[a]	95% CI	p
Separation from parents	3.75	1.30–10.81	0.015	1.43	0.43–4.78	0.559
Child abuse	2.49	0.91–6.80	0.075	1.55	0.62–3.91	0.349
Exposure to domestic violence	10.47	2.85–38.49	<0.001	6.23	1.44–26.92	0.014

[a] Adjusted for lifetime substance use disorders and PCL:SV score.

3.5. Childhood adversity, conduct disorder and violence

Of the patients who had the greatest lifetime propensity to violence (GRVS score of 4), prior CD was present in 75%. CD symptoms were significantly associated with later propensity to violence after adjusting for lifetime substance use disorders (see Table 3). The cumulative number of childhood adversities was associated both with number of CD symptoms and the adult propensity to violence (see Table 3). Analyses were conducted to explore the hypothesis that CD was a mediator of the association between cumulative childhood adversities and violence. CD symptoms were added to the regression model as a covariate, and as shown in the brackets in Fig. 1, the association between childhood adversity and violence was no longer statistically significant. The attenuation of this association, therefore suggests that CD may mediate the association between cumulative childhood adversities and adult violence, indicating an indirect pathway between them.

4. Discussion

In this study of men with schizophrenia, 94% of the most violent patients had experienced at least one form of childhood adversity. Exposure to domestic violence during childhood was associated with an increased propensity to violence in adulthood. The cumulative number of childhood adversities was associated with adult propensity to violence and attenuation of this association suggested that CD may be a mediator of the relationship.

4.1. Childhood adversity and conduct disorder

Child abuse and separation from a parent were associated with CD, which is consistent with previous evidence (Afifi et al., 2011), though prospective studies are needed to confirm the temporality of the relationship and explore aetiological links. For example, the trauma of child abuse may cause behaviour that could place a child at greater likelihood of developing CD, or the difficult behaviour of CD may place these children at an increased risk of being abused or maltreated.

4.2. Childhood adversity and violence in adulthood

The prevalence of witnessing domestic violence in childhood was 26% in our sample and may be as high as 49% in some schizophrenia cohorts (Rosenberg et al., 2007), compared to 12.5% among the general population (Felitti et al., 1998). Witnessing domestic violence during childhood was associated with later violent behaviour in adulthood. The effect size remained large even after adjusting for lifetime substance use and psychopathy. Although most patients who witnessed domestic violence also experienced at least one other childhood adversity and adverse childhood experiences are strongly interrelated (Felitti et al., 1998), the association with violence remained significant after controlling for these other adversities. This indicates that the association is specific to domestic violence, rather than reflecting wider childhood adversities.

It is unclear why domestic violence appears to be more strongly associated with later violence than the other types of childhood adversity. Social learning theory proposes that those children who witness domestic violence may engage in violence due to modelling behaviour effects (Casiano et al., 2009). Hence, the act of seeing others engage in violent acts at home may normalise this behaviour and justify aggressive strategies when angry, and perhaps especially if self-control is compromised by a psychotic illness. We are not aware of any other studies that have specifically demonstrated an association between exposure to domestic violence in childhood and violent behaviour in adulthood in patients with schizophrenia.

Table 3
Childhood adversity, conduct disorder symptoms and propensity to violence.

Variables	AOR[a]	95% CI	p
Violence and conduct disorder symptoms	1.32	1.09–1.60	0.004
Cumulative childhood adversities and violence	1.90	1.11–3.26	0.020
Cumulative childhood adversities and conduct disorder symptoms	1.26	1.06–1.50	0.009

[a] Adjusted for lifetime substance use disorders.

4.3. Childhood adversity, conduct disorder and violence

This study has shown that each CD symptom present before the age of 15 is associated with an increased propensity to violence in adulthood. This is consistent with the results of an earlier study of men and women with severe mental illness (Hodgins et al., 2008) and another of men with schizophrenia spectrum disorders (Hodgins et al., 2005), where the number of CD symptoms present before the age of 15 significantly increased the risk of violent crime, independently of alcohol and illicit drug use.

This study suggests a cumulative effect of childhood adversities on lifetime propensity for violence. A cumulative effect of childhood traumas on the risk of violence in adulthood among those who develop psychosis has been reported previously (Bosqui et al., 2014). Our study has developed this further by suggesting that CD may mediate the association between cumulative childhood adversity and violence in adulthood among men with schizophrenia. This is consistent with a recent study of men with severe mental illness, where the presence of CD before the age of 12 and antisocial personality disorder in adulthood, was considered to mediate the relationship found between childhood trauma and recent violent acts (Bruce and Laporte, 2015). This raises the question of whether CD is a component of complex interactions between various factors in a developmental pathway towards adult violence.

4.4. Hypothetical developmental pathway

In this sample of men with schizophrenia 44% met criteria for prior CD, a finding strikingly consistent with previous studies of in-patients with severe mental illness (Hodgins et al., 2008) and those with schizophreniform disorder (Kim-Cohen et al., 2003). Both schizophrenia (Murray and Lewis, 1988) and CD (Blair et al., 2014) are neurodevelopmental disorders, where a combination of genetic and environmental factors interact to modify the normal trajectory of brain development and behaviour. From an aetiological perspective one possible explanation for why CD is more common among people with schizophrenia than the general population, is that a proportion of factors that influence the risk of developing each disorder are common between them. For example, there is evidence that childhood physical abuse is more common in those who develop severe mental illness and is also more common among those with a history of CD (Hodgins et al., 2008), leading to the hypothesis that physical abuse is important in the aetiology of both. It has been proposed that there are shared causative risk factors for schizophrenia and CD, and possibly a distinct pattern of neural development (Hodgins et al., 2014).

The mechanisms by which childhood adversity increases vulnerability to psychopathology remain poorly understood and are likely to involve complex interactions (McCrory et al., 2012). A developmental perspective will be crucial in understanding the pathway from childhood vulnerability, via adversity, to later violence among men with schizophrenia. One node on the pathway may be childhood adversity increasing the risk of CD (and schizophrenia), which then increases the risk of substance misuse (Malcolm et al., 2011), perhaps earlier than in the general population, and at a more critically sensitive point in the brain's development, which then further increases the risk of schizophrenia (Di Forti et al., 2015) and behaving violently (Witt et al., 2013). It is clear that prospective longitudinal studies are needed to explore if there is a common developmental pathway from childhood

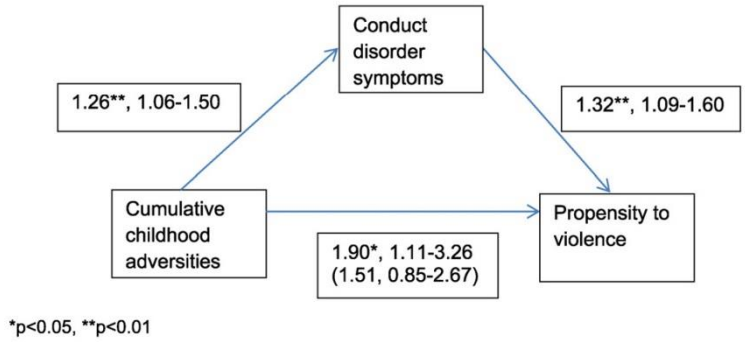

Fig. 1. Cumulative childhood adversities, conduct disorder symptoms and propensity to violence. Numbers shown are OR adjusted for lifetime substance use disorders and their 95% confidence intervals. Numbers in the brackets are the OR when CD symptoms were added to the regression model.

adversity, through CD, and drug use to schizophrenia, and finally violence.

4.5. Strengths and limitations

This study included data on a uniquely well-defined clinical sample of men with schizophrenia who were drawn from a wide range of in-patient and out-patient clinical services. The participants were comprehensively assessed, both in terms of their background history, generally and as it related to violence, and their mental disorders. The use of the GRVS allowed for the objective quantification of the patients' lifetime propensity to violence.

This study is limited by its cross-sectional design, which did not allow temporal proximity between the measurement of the clinical variables and the violent behaviour. It was not possible to test the contribution of CD only, compared to CD progressing to ASPD, on lifetime propensity to violence as there were only three patients in the sample with CD only. It is also important to note in terms of temporality, that childhood adversity occurring before the age of 17 was assessed and so these events did not necessarily pre-date CD symptoms which were measured prior to the age of 15.

Retrospective recall bias is a relevant consideration in studies of this type, as CD, violence and childhood adversities were all measured retrospectively using self-report. However, corroborating information was obtained from medical records for all participants and family informants where available. Good convergent and concurrent validity and reliability has previously been established for the tool we utilised to assess childhood adversities (Fisher et al., 2011). However, some have expressed wider concerns about the potential bias of self-report of childhood abuse in those with mental disorders (Susser and Widom, 2012). Self-report of violence has been shown to be reliable and valid, with patients reporting 5 times more violent acts than those documented in official records (Steadman et al., 1998). It is possible that the prevalence of comorbid CD and ASPD in our sample may adversely affect the reliability of self-report in our sample, as deceitfulness is part of the diagnostic criteria for both CD and ASPD.

5. Conclusions

Exposure to domestic violence during childhood was associated with violent behaviour in adulthood among men with schizophrenia. As far as we are aware, this is the first time this finding has been demonstrated. The association between cumulative childhood adversities and propensity to violence may be mediated by CD. This study emphasises the importance of developmental pathways to violence among men with schizophrenia. Further work is needed to advance our understanding of the complex interplay between a variety of childhood risk factors that may be aetiologically important to the future risk of both violence and schizophrenia.

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Contributors

All authors were involved in the study design. CO and SH recruited and assessed the participants. CO conducted these statistical analyses and wrote the first draft of this manuscript. All authors contributed to and have approved this manuscript.

Conflict of interest

No authors have a conflict of interest to declare.

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References

Afifi, T.O., McMillan, K.A., Asmundson, G.J.G., Pietrzak, R.H., Sareen, J., 2011. An examination of the relation between conduct disorder, childhood and adulthood traumatic events, and posttraumatic stress disorder in a nationally representative sample. J. Psychiatr. Res. 45 (12), 1564–1572.

Appelbaum, P., 2008. Foreword. In: Simon, R., Tardiff, K. (Eds.), Textbook of Violence Assessment and Management. American Psychiatric Publishing Inc., Washington, DC, pp. xvii–xxix.

Appelbaum, P., Robbins, P., Monahan, J., 2000. Violence and delusions: data from the MacArthur violence risk assessment study. Am. J. Psychiatr. 157, 566–572.

Arseneault, L., Moffitt, T., Caspi, A., Taylor, P., Silva, P., 2000. Mental disorders and violence in a total birth cohort: results from the Dunedin study. Arch. Gen. Psychiatry 57, 979–986.

Bennouna-Greene, M., Bennouna-Greene, V., Berna, F., Defranoux, L., 2011. History of abuse and neglect in patients with schizophrenia who have a history of violence. Child Abuse Negl. 35 (5), 329–332.

Bifulco, A., Bernazzani, O., Moran, P., Jacobs, C., 2005. The childhood experience of care and abuse questionnaire (CECA.Q): validation in a community series. Br. J. Clin. Psychol. 44, 563–581.

Blair, R.J.R., Leibenluft, E., Pine, D.S., 2014. Conduct disorder and callous-unemotional traits in youth. N. Engl. J. Med. 371 (23), 2207–2216.

Bo, S., Abu-Akel, A., Kongerslev, M., Haahr, U.H., Simonsen, E., 2011. Risk factors for violence among patients with schizophrenia. Clin. Psychol. Rev. 31 (5), 711–726.

Bosqui, T.J., Shannon, C., Tiernan, B., Beattie, N., Ferguson, J., Mulholland, C., 2014. Childhood trauma and the risk of violence in adulthood in a population with a psychotic illness. J. Psychiatr. Res.

Bruce, M., Laporte, D., 2015. Childhood trauma, antisocial personality typologies and recent violent acts among inpatient males with severe mental illness: exploring an explanatory pathway. Schizophr. Res. 162 (1–3), 285–290.

Casiano, H., Mota, N., Afifi, T.O., Enns, M.W., Sareen, J., 2009. Childhood maltreatment and threats with weapons. J. Nerv. Ment. Dis. 197 (11), 856–861.

Daffern, M., Howells, K., Ogloff, J., Lee, J., 2005. Individual characteristics predisposing patients to aggression in a forensic psychiatric hospital. J. Forensic Psychiatry Psychol. 16 (4), 729–746.
Dean, K., Walsh, E., Morgan, C., Demjaha, A., Dazzan, P., Morgan, K., Lloyd, T., Fearon, P., Jones, P.B., Murray, R.M., 2007. Aggressive behaviour at first contact with services: findings from the AESOP first episode psychosis study. Psychol. Med. 37 (4), 547–557.
Di Forti, M., Marconi, A., Carra, E., Fraietta, S., Trotta, A., Bonomo, M., Bianconi, F., Gardner-Sood, P., O'Connor, J., Russo, M., Stilo, S.A., Marques, T.R., Mondelli, V., Dazzan, P., Pariante, C., David, A.S., Gaughran, F., Atakan, Z., Iyegbe, C., Powell, J., Morgan, C., Lynskey, M., Murray, R.M., 2015. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: a case–control study. Lancet Psychiatry 2 (3), 233–238.
Douglas, K.S., Guy, L.S., Hart, S.D., 2009. Psychosis as a risk factor for violence to others: a meta-analysis. Psychol. Bull. 135 (5), 679–706.
Elbogen, E., Johnson, S., 2009. The intricate link between violence and mental disorder: results from the National Epidemiologic Survey on Alcohol and Related Conditions. Arch. Gen. Psychiatry 66, 152–161.
Fazel, S., Langstrom, N., Hjern, A., Grann, M., Lichtenstein, P., 2009. Schizophrenia, substance abuse and violent crime. JAMA 301, 2016–2023.
Felitti, V.J., Anda, R.F., Nordenberg, D., Williamson, D.F., Spitz, A.M., Edwards, V., Koss, M.P., Marks, J.S., 1998. Relationship of childhood abuse and household dysfunction to many of the leading causes of death in adults: the adverse childhood experiences (ACE) study. Am. J. Prev. Med. 14 (4), 245–258.
First, M., Gibbon, M., Spitzer, R., Williams, J., Benjamin, L., 1997. User's Guide for the Structured Clinical Interview for DSM-IV Axis II Personality Disorders: SCID-II. American Psychiatric Publishing, Washington.
First, M., Spitzer, R., Gibbon, M., Williams, J., 2002. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version. Patient ed. New York State Psychiatric Institute, New York.
Fisher, H.L., Craig, T.K., Fearon, P., Morgan, K., Dazzan, P., Lappin, J., Hutchinson, G., Doody, G.A., Jones, P.B., McGuffin, P., Murray, R.M., Leff, J., Morgan, C., 2011. Reliability and comparability of psychosis patients' retrospective reports of childhood abuse. Schizophr. Bull. 37 (3), 546–553.
Foley, D.L., Eaves, L.J., Wormley, B., Silberg, J.L., Maes, H.H., Kuhn, J., Riley, B., 2004. Childhood adversity, monoamine oxidase A genotype, and risk for conduct disorder. Arch. Gen. Psychiatry 61 (7), 738–744.
Gardner, D., Murphy, A., O'Donnell, H., Centorrino, F., Baldessarini, R., 2010. International consensus study of antipsychotic dosing. Am. J. Psychiatry 167, 686–693.
Gibbon, S., Ferriter, M., Duggan, C., 2009. A comparison of the family and childhood backgrounds of hospitalised offenders with schizophrenia or personality disorder. Crim. Behav. Ment. Health 19, 207–218.
Gunn, J., Robertson, G., 1976. Drawing a criminal profile. Br. J. Criminol. 16 (2), 156–160.
Guy, L.S., Douglas, K.S., 2006. Examining the utility of the PCL:SV as a screening measure using competing factor models of psychopathy. Psychol. Assess. 18 (2), 225–230.
Harris, A.W.F., Large, M.M., Redoblado-Hodge, A., Nielssen, O., Anderson, J., Brennan, J., 2010. Clinical and cognitive associations with aggression in the first episode of psychosis. Aust. N. Z. J. Psychiatry 44 (1), 85–93.
Harris, S., Oakley, C., Picchioni, M., 2013. Quantifying violence in mental health research. Aggress. Violent Behav. 18, 695–701.
Hart, S., Cox, D., Hare, R., 1995. The Hare Psychopathy Checklist: Screening Version (PCL: SV). Multi-Health Systems, Toronto.
Heads, T., Taylor, P., Leese, M., 1997. Childhood experiences of patients with schizophrenia and a history of violence: a special hospital sample. Crim. Behav. Ment. Health 7, 117–130.
Hepgul, N., Pariante, C.M., Dipasquale, S., Diforti, M., Taylor, H., Marques, T.R., Morgan, C., Dazzan, P., Murray, R.M., Mondelli, V., 2012. Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. Psychol. Med. 42 (9), 1893–1901.
Hodgins, S., Hiscoke, U., Freese, R., 2003. The antecedents of aggressive behavior among men with schizophrenia: a prospective investigation of patients in community treatment. Behav. Sci. Law 21, 523–546.
Hodgins, S., Tiihionen, J., Ross, D., 2005. The consequences of conduct disorder for males who develop schizophrenia: associations with criminality, aggressive behaviour, substance use and psychiatric services. Schizophr. Res. 78, 323–335.
Hodgins, S., Cree, A., Alderton, J., Mak, T., 2008. From conduct disorder to severe mental illness: associations with aggressive behaviour, crime and victimization. Psychol. Med. 38, 975–987.
Hodgins, S., Piatosa, M.J., Schiffer, B., 2014. Violence among people with schizophrenia: phenotypes and neurobiology. Curr. Top. Behav. Neurosci. 17, 329–368.
Hoptman, M.J., Yates, K.F., Patalinjug, M.B., Wack, R.C., Convit, A., 1999. Clinical prediction of assaultive behavior among male psychiatric patients at a maximum-security forensic facility. Psychiatr. Serv. 50 (11), 1461–1466.
Kay, S., Fiszbein, A., Opler, L., 1987. The positive and negative syndrome scale for schizophrenia (PANSS). Schizophr. Bull. 13, 261–276.
Kelleher, I., Keeley, H., Corcoran, P., Ramsay, H., Wasserman, C., Carli, V., Sarchiapone, M., Hoven, C., Wasserman, D., 2013. Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. Am. J. Psychiatr. 170, 734–741.
Kim-Cohen, J., Caspi, A., Moffitt, T.E., Harrington, H., Milne, B.J., Poulton, R., 2003. Prior juvenile diagnoses in adults with mental disorder: developmental follow-back of a prospective-longitudinal cohort. Arch. Gen. Psychiatry 60 (7), 709–717.
Krakowski, M., Czobor, P., Chou, J., 1999. Course of violence in patients with schizophrenia: relationship to clinical symptoms. Schizophr. Bull. 25, 505–517.
Large, M.M., Nielssen, O., 2011. Violence in first-episode psychosis: a systematic review and meta-analysis. Schizophr. Res. 125 (2–3), 209–220.
Link, B., Stueve, A., 1994. Psychotic symptoms and the violent/illegal behaviour of mental patients compared to the community. In: Monahan, J., Steadman, H. (Eds.), Violence and Mental Disorder: Development in Risk Assessment. University of Chicago Press, Chicago.
Malcolm, C.P., Picchioni, M.M., DiForti, M., Sugranyes, G., Cooke, E., Joseph, C., McQueen, G., Paparelli, A., Stilo, S., O'Connor, J., Morgan, C., Murray, R.M., Hodgins, S., 2011. Pre-morbid conduct disorder symptoms are associated with cannabis use among individuals with a first episode of psychosis. Schizophr. Res. 126 (1–3), 81–86.
Maniglio, R., 2015. Significance, nature, and direction of the association between child sexual abuse and conduct disorder: a systematic review. Trauma Violence Abuse 16 (3), 241–257.
McCrory, E., De Brito, S.A., Viding, E., 2012. The link between child abuse and psychopathology: a review of neurobiological and genetic research. J. R. Soc. Med. 105 (4), 151–156.
Morgan, C., Kirkbridge, J., Leff, J., Craig, T., Hutchinson, G., McKenzie, K., Morgan, K., Dazzan, P., Doody, G.A., Jones, P., Murray, R., Fearon, P., 2007. Parental separation, loss and psychosis in different ethnic groups: a case–control study. Psychol. Med. 37, 495–503.
Morgan, C., Reininghaus, U., Reichenberg, A., Frissa, S., Hotopf, M., Hatch, S.L., 2014. Adversity, cannabis use and psychotic experiences: evidence of cumulative and synergistic effects. Br. J. Psychiatry 204 (5), 346–353.
Murray, R.M., Lewis, S.W., 1988. Is schizophrenia a neurodevelopmental disorder? Br. Med. J. (Clin. Res. Ed.) 296 (6614), 63.
Rosenberg, S., Lu, W., Mueser, K., Jankowski, M., Cournos, F., 2007. Correlates of adverse childhood events among adults with schizophrenia spectrum disorders. Psychiatr. Serv. 58, 245–253.
Sarchiapone, M., Carli, V., Cuomo, C., Marchetti, M., Roy, A., 2009. Association between childhood trauma and aggression in male prisoners. Psychiatry Res. 165, 187–192.
Short, T., Thomas, S., Mullen, P., Ogloff, J.R.P., 2013. Comparing violence in schizophrenia patients with and without comorbid substance-use disorders to community controls. Acta Psychiatr. Scand.
Steadman, H.J., Mulvey, E.P., Monahan, J., Robbins, P.C., Appelbaum, P.S., Grisso, T., Roth, L.H., Silver, E., 1998. Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. Arch. Gen. Psychiatry 55 (5), 393–401.
Stompe, T., Ortwein-Swoboda, G., Schanda, H., 2004. Schizophrenia, delusional symptoms, and violence: threat/control-override concept re-examined. Schizophr. Bull. 30, 31–44.
Susser, E., Widom, C.S., 2012. Still searching for lost truths about the bitter sorrows of childhood. Schizophr. Bull. 38 (4), 672–675.
Swanson, J., Swartz, M., Van Dorn, R., Elbogen, E., Wagner, H., Rosenheck, R., Stroup, T., McEvoy, J., Lieberman, J., 2006. A national study of violent behaviour in persons with schizophrenia. Arch. Gen. Psychiatry 63, 490–499.
Swanson, J., van Dorn, R., Swartz, M., Smith, A., Elbogen, E., Monahan, J., 2008. Alternative pathways to violence in persons with schizophrenia: the role of childhood antisocial behaviour problems. Law Hum. Behav. 32, 228–240.
Tengström, A., Hodgins, S., Grann, M., Långström, N., Kullgren, G., 2004. Schizophrenia and criminal offending: the role of psychopathy and substance use disorders. Crim. Just. Behav. 31 (4), 367–391.
Ullrich, S., Keers, R., Coid, J., 2014. Delusions, anger and serious violence: new findings from the MacArthur violence risk assessment study. Schizophr. Bull. 40, 1174–1181.
Van Dorn, R., Volavka, J., Johnson, N., 2012. Mental disorder and violence: is there a relationship beyond substance use? Soc. Psychiatry Psychiatr. Epidemiol. 47 (3), 487–503.
Varese, F., Smeets, F., Drukker, M., Lieverse, R., Lataster, T., Viechtbauer, W., Read, J., Van Os, J., Bentall, R.P., 2012. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective-and cross-sectional cohort studies. Schizophr. Bull. 38 (4), 661–671.
Villodas, M.T., Litrownik, A.J., Thompson, R., Jones, D., Roesch, S.C., Hussey, J.M., Block, S., English, D.J., Dubowitz, H., 2014. Developmental transitions in presentations of externalizing problems among boys and girls at risk for child maltreatment. Dev. Psychopathol. 27 (1), 205–219.
Volavka, J., 2014. Comorbid personality disorders and violent behavior in psychotic patients. Psychiatry Q. 85 (1), 65–78.
Volavka, J., Citrome, L., 2011. Pathways to aggression in schizophrenia affect results of treatment. Schizophr. Bull. 37, 921–929.
Walsh, E., Buchanan, A., Fahy, T., 2002. Violence and schizophrenia: examining the evidence. Br. J. Psychiatry 180, 490–495.
Witt, K., van Dorn, R., Fazel, S., 2013. Risk factors for violence in psychosis: systematic review and meta-regression analysis of 110 studies. PLoS One 8 (2).

6.2 Conduct disorder as a mediator of the association between cumulative childhood adversities and violence

The published paper above found that cumulative childhood adversities were associated with propensity to violence and this association may be mediated by CD. A mediation model seeks to explain what underlies a relationship between an independent variable and a dependent variable by the inclusion in the model of a third variable (the mediator variable). Rather than a direct causal relationship between the independent and dependent variable, a mediation model proposes that the independent variable influences the mediator variable (in this case CD symptoms), which in turn influences the dependent variable.

The results in the paper show that cumulative childhood adversities were associated with propensity to violence (odds ratio 1.90). CD symptoms were then added to the regression model as a co-variate, to explore whether CD symptoms were a mediator of this association. As shown in the brackets in figure 1 in the published paper, the association between childhood adversities and violence was then no longer statistically significant. This substantial attenuation in the effect size of the association between childhood adversities and violence after co-variation of the mediator variable (CD symptoms), was interpreted as evidence of an indirect pathway, rather than a direct causal relationship between childhood adversities and violence. In other words, that childhood adversity via conduct disorder may be a pathway to violent behaviour in schizophrenia. This raises the question of whether CD and childhood adversities are part of complex interactions, possibly with other factors in childhood, which contribute to an increased propensity to violence in adulthood.

6.3 Conclusions

This is the first study to demonstrate that among men with schizophrenia, exposure to domestic violence in childhood is associated with an increased propensity to violence in adulthood. Symptoms of CD were associated with cumulative exposure to childhood adversities. Conduct disorder may mediate the association between cumulative childhood adversities and adult propensity to violence, indicating an indirect pathway. These results indicate a complex

interplay between CD, childhood adversity and later violence in schizophrenia. There may be shared aetiological risk factors in childhood which contribute to a pathway to violence.

Chapter 7 Conduct disorder, substance misuse and propensity to violence in schizophrenia

7.1 Abstract

Substance misuse is an important factor associated with an increased risk of violent behaviour in patients with schizophrenia. Pre-morbid conduct disorder is also a marker for those more likely to pose an adult risk of violence. This chapter aimed to explore the relationships between conduct disorder and substance misuse in order to inform our model of the link between schizophrenia and violence. Fifty-four male patients with schizophrenia were recruited from a broad range of inpatient and outpatient mental health services. Symptoms of conduct disorder prior to the age of 15, use of alcohol and drugs, and adult violent behaviour were quantified. Patients with schizophrenia and pre-morbid conduct disorder began using alcohol and cannabis at an earlier age and more frequently than those without. Those with pre-morbid conduct disorder also had higher rates of lifetime substance use disorders. Pre-morbid conduct disorder and lifetime substance use disorders were both significantly associated with an increased propensity to violence in men with schizophrenia. Both conduct disorder and substance use disorders play independent roles in the propensity to violence but also interact with each other. Conduct disorder and early substance misuse may be useful targets for early intervention to reduce the risk of future violence in schizophrenia.

7.2 Background

The literature relating to substance misuse and violence in schizophrenia has been reviewed in section 2.5. To summarize, substance misuse is associated with violence both in the general population (Coid et al., 2006) and in those living with schizophrenia (Swanson et al., 2006), though controversy remains about the extent of its role in mediating the risk of violence in schizophrenia. Some evidence shows that substance misuse is one of multiple factors that increase the risk of violent behaviour in patients with psychotic illnesses (Daffern et al., 2005, Harris et al., 2010, Stompe et al., 2004); while other data suggest that the increased risk of violence is primarily mediated by co-occurring substance misuse, with a much lesser role for

other factors (Elbogen and Johnson, 2009, Fazel et al., 2009). Adding complexity to this debate, a reanalysis of data from one of these studies (Elbogen and Johnson, 2009) found that those with severe mental illness, irrespective of the presence of substance abuse, were significantly more likely to be violent than those with no mental illness (Van Dorn et al., 2012), a finding later confirmed specifically for schizophrenia (Short et al., 2013). In short, it is now generally accepted that there is an increased risk of violence in schizophrenia, independent of co-morbid substance misuse, though substance misuse is associated with a further increase in that risk.

The nature of the link between schizophrenia, substance misuse and violence may involve a complex interaction with other vulnerabilities, such as pre-morbid conduct disorder (CD). CD reflects a pattern of early life persistent antisocial behaviour that begins before the age of 15, symptoms include: initiating physical fights; forcing someone into sexual activity; being physically cruel to animals; deliberately destroying others' property; fire-setting with the intention of causing serious damage (First et al., 1997). Substance misuse is itself not a diagnostic criterion for CD, though CD is associated with an increased risk of substance abuse (Blair et al., 2014) and an increased risk of starting to use all classes of substances before the age of 18 (Hopfer et al., 2013). Furthermore from a developmental perspective, CD is over-represented in the childhood histories of patients who later develop schizophrenia (Hodgins et al., 2008, Kim-Cohen et al., 2003) and finally is then associated with an increased risk of adult violent behaviour (Arseneault et al., 2000, Hodgins et al., 2008, Swanson et al., 2008). It may be that substance misuse is more common in patients with schizophrenia with pre-morbid CD (Hodgins et al., 2005). Furthermore it is not clear if these links are somehow aetiologically connected through childhood or adolescence, or are merely external behavioural markers at each developmental stage of those patients with schizophrenia who will be more violent as adults.

7.3 Hypotheses

It was hypothesised that among patients with schizophrenia and pre-morbid CD, compared to those without CD, there would be:

1) use of alcohol and drugs at an earlier age

2) a greater frequency of alcohol and drug use before adulthood

3) higher rates of lifetime substance use disorders which would then be associated with an increased propensity to violence.

7.4 Specific methodology

The methodology is described in chapter 4 and the additional questionnaire utilized to obtain information about alcohol and drug use is appendix B. The Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (First et al., 2002) was used to diagnose misuse of alcohol and drugs. The fourth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) categorizes 'substance use disorders' as either abuse or dependence (American Psychiatric Association, 2000).

7.5 Results

7.5.1 Sample characteristics

The demographics of the patient group are as described in chapter 5; all patients took part in this component of the study.

7.5.2 Associations with violence

There was no association between age, ethnicity or current psychotic symptoms and lifetime propensity to violence (GRVS score). CD (OR=5.24, CI 1.61-17.04, p=0.006), ASPD (OR=5.57, CI 1.70-18.19, p=0.004) and PCL:SV score (OR=1.37, CI 1.18-1.58, p<0.001) were all associated with violence. There was moderate correlation between symptoms of CD, and ASPD, and PCL:SV, suggesting a degree of co-linearity entirely consistent with their clinical constructs. Therefore, PCL:SV score was included in the models as it was the most strongly associated of the three variables with violence propensity rated on the GRVS score. The earlier analyses in chapter 6 identified that cumulative childhood adversity was associated with violence (Oakley et al., 2016) and so this variable was also entered into the regression models.

7.5.3 Substance use disorders and conduct disorder

7.5.3.1 Age of onset and frequency of early use

Patients with schizophrenia and pre-morbid CD, compared to those without pre-morbid CD, first used alcohol at an earlier age (12.1 years vs 15.1 years, U=512.50, p=0.001). Cannabis (but not other drugs) use also started younger in the CD group (13.26 years vs 15.53 years, U=308.00, p=0.023). CD was also associated with a greater frequency of alcohol and cannabis use both before the age of 15 and between 15 and 18 years old (table 7-1 and figures 7-1, 7-2, 7-3 & 7-4).

Table 7-1 Comparison of frequency of alcohol and cannabis use in those with and without pre-morbid conduct disorder

Frequency of use	**Test statistic** (X^2)	**Significance** (p)
Alcohol before 15 years old	13.33 (df=4)	0.010
Alcohol between 15 and 18 years old	16.59 (df=4)	0.002
Cannabis before 15 years old	16.72 (df=4)	0.002
Cannabis between 15 and 18 years old	7.87 (df=3)	0.049

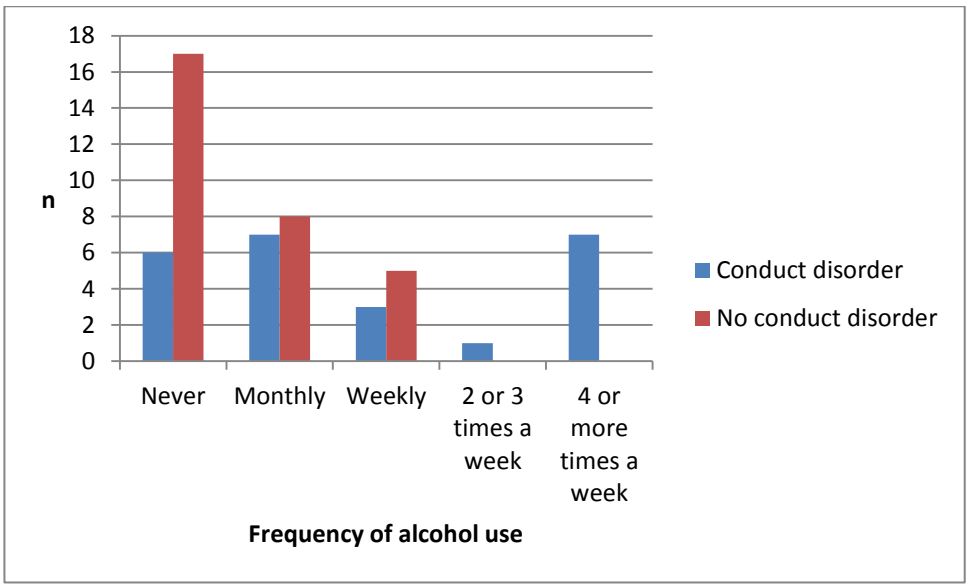

Figure 7-1 Frequency of alcohol use before 15 years old in participants with schizophrenia (n=54)

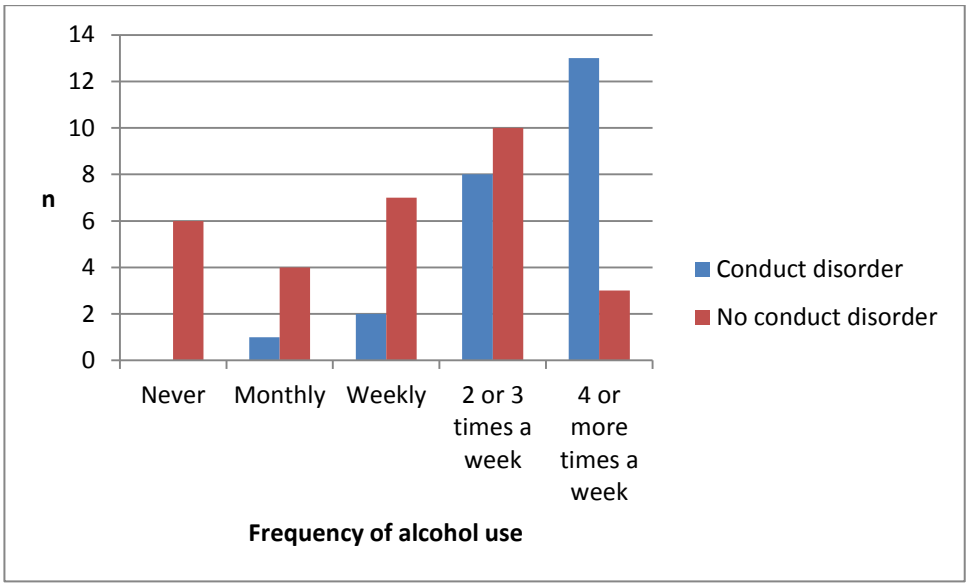

Figure 7-2 Frequency of alcohol use between 15 and 18 years old in participants with schizophrenia (n=54)

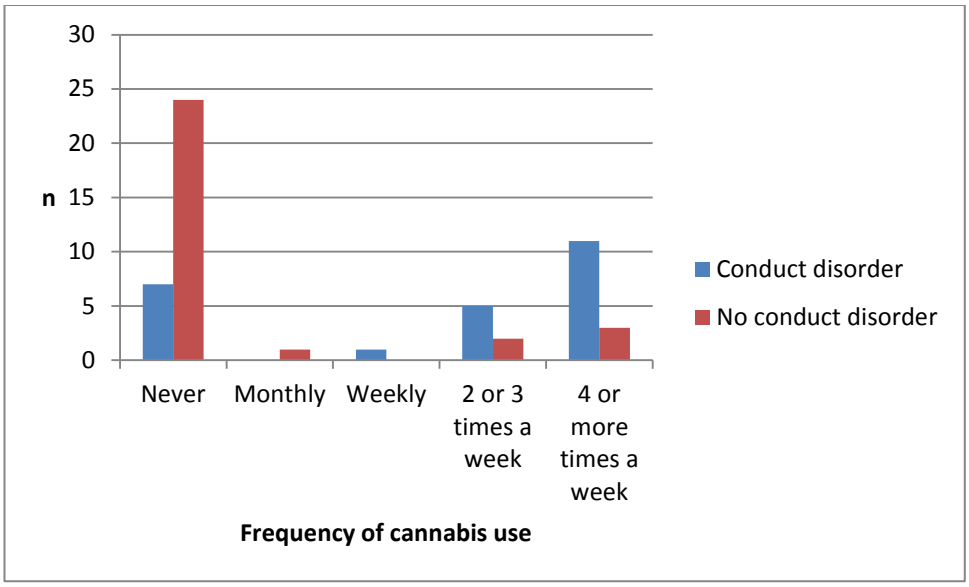

Figure 7-3 Frequency of cannabis use before 15 years old in participants with schizophrenia (n=54)

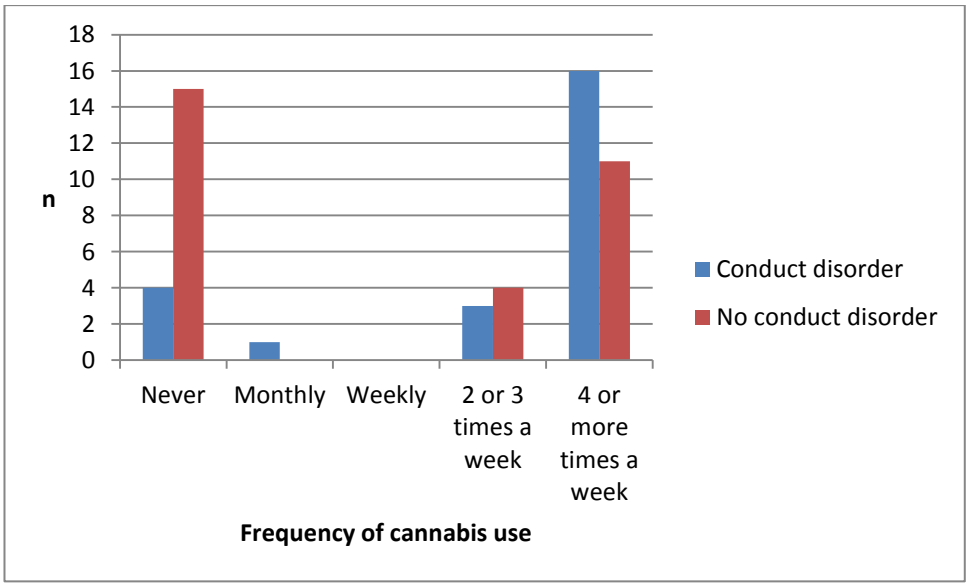

Figure 7-4 Frequency of cannabis use between 15 and 18 years old in participants with schizophrenia (n=54)

7.5.3.2 Lifetime history

There were also higher rates of lifetime substance use disorder (SUD) in the patients with pre-morbid CD (table 7-2). All the patients with pre-morbid CD had at least one lifetime SUD (96% had an alcohol use disorder and 92% had a drug use disorder). Of those without CD, 63% had a lifetime history of a SUD (43% had an alcohol use disorder and 53% had a drug use disorder). Patients with CD were more likely to use more types of drugs (4.33 drugs vs 1.80 drugs, U=134, p<0.001).

Table 7-2 Lifetime history of substance use disorders and pre-morbid conduct disorder

	Patients with CD (n=24)	**Patients without CD** (n=30)	**Test statistic** (X^2) (df=1)	**Significance** (p)
Alcohol use disorder	23	13	16.54	<0.001
Cannabis use disorder	22	16	9.40	0.002
Cocaine use disorder	16	5	14.03	<0.001
Opioid use disorder	11	1	13.93	<0.001
Stimulant use disorder	11	3	8.92	0.003

7.5.4 Substance misuse, conduct disorder and violence

Conduct disorder was significantly positively associated with propensity to violence after adjusting for lifetime SUD and cumulative childhood adversity (OR=3.89, 95%CI 1.14-13.28, p=0.03). Of the 16 patients who had the greatest lifetime propensity to violence (GRVS score of 4), pre-morbid CD was present in 75% and a lifetime history of SUD in 100%. Of the 4 patients who had the lowest lifetime propensity to violence (GRVS score of 0), none had pre-morbid CD or a lifetime history of SUD. Of the 11 patients without pre-morbid CD or SUD, all had low GRVS scores of between 0 and 2.

A history of an alcohol related arrest was strongly associated with an increased propensity to violence (OR=8.12, 95% CI 2.10-31.43, p=0.002). Twenty-three participants (43%) reported behaving violently when under the influence of alcohol and 20 (37%) said they had been the victim of violence when drunk. In the whole group, a lifetime history of a SUD was associated with an increased propensity to violence, after adjusting for PCL:SV score and cumulative childhood adversity (OR=6.54, 95%CI 1.13-37.79, p=0.036). When considered separately, there was a trend between alcohol use disorders and propensity to violence (p=0.071) but not for drug use disorders.

The relationship between SUD and violence was assessed in groups with and without pre-morbid CD. All of the patients with CD had a lifetime history of SUD and so SUD did not distinguish those with a greater or lesser propensity to violence. In the group without CD, lifetime SUD was still associated with GRVS, after adjusting for PCL:SV score, (p=0.036) but this was only a trend after also adjusting for cumulative childhood adversity (p=0.061).

7.6 Discussion

This study of men with schizophrenia has shown that patients with pre-morbid CD had higher rates of lifetime SUD and began using alcohol and cannabis earlier and more frequently and used a wider variety of drugs. A lifetime history of SUD was associated with an increased propensity to violence. A trend remained between SUD and violence when I considered only the group of patients who did not have pre-morbid CD, suggesting the importance of SUD in violence even in the absence of CD. In addition, CD was associated with an increased propensity to violence, after adjusting for SUD. These findings confirm that both CD and SUD are independently associated with an increased risk of violence in schizophrenia.

7.6.1 Substance use disorders and conduct disorder

Cannabis use is associated with the subsequent development of psychotic symptoms and disorders, with the frequency and quantity of cannabis use influencing the strength of that

association (Zammit et al., 2002, Arseneault et al., 2004, Di Forti et al., 2015). Cannabis use in early adolescence is more strongly associated with experiencing symptoms of schizophrenia in adulthood than use in late adolescence (Arseneault et al., 2002). It has also been suggested that CD symptoms may independently increase the likelihood of cannabis use, which in turn increases the risk of psychosis (Malcolm et al., 2011).

In this study patients with schizophrenia and pre-morbid CD began using alcohol and cannabis at an earlier age and with greater frequency than those without pre-morbid conduct disorder. This is consistent with evidence that among patients with a first episode of psychosis, the number of CD symptoms is linked to exposure to cannabis at a younger age (Malcolm et al., 2011). Also, in patients with schizophrenia, a history of CD is associated with an earlier age of onset and more severe symptoms of substance abuse (Mueser et al., 1997, Fulwiler et al., 1997). Patients with pre-morbid CD in this study also had an increased rate of lifetime SUD, which fits with previous evidence (Mueser et al., 2006).

7.6.2 Substance use disorders, conduct disorder and violence

Our finding that CD present before the age of 15 is associated with an increased propensity to adult violence, after adjusting for lifetime SUD, is in keeping with the results of earlier studies (Hodgins et al., 2005, Hodgins et al., 2008). This highlights the importance of considering pre-morbid CD in the association between schizophrenia and violence, independently of alcohol and illicit drug use. However, it is clear that lifetime substance misuse is also crucially important independent of CD. In this sample, a lifetime history of a SUD was associated with an increased propensity to violence in schizophrenia, and there was also a trend towards this when considering only those patients who did not have pre-morbid CD. Therefore, both CD and SUD independently increase the propensity to violence.

Earlier studies have shown an association between current alcohol abuse and violence in first episode psychosis (Volavka et al., 1997, Steinert et al., 1999). Other studies in first episode

psychosis have found previous drug (but not alcohol) misuse was associated with aggression (Dean et al., 2007, Harris et al., 2010, Fazel et al., 2014, Langeveld et al., 2014). However, although all of these studies considered past offending, none assessed CD or ASPD. We have shown that pre-morbid CD is associated with an increased risk of lifetime drug use disorders. It is therefore possible that CD is influencing the association between drug use and violence found in those studies (which did not assess CD). Indeed it has been demonstrated that individuals with cannabis dependence are more likely to be violent and this association was best explained by a history of conduct disorder (Arseneault et al., 2000).

CD occurring prior to the onset of psychosis has an effect both on risk of substance abuse and the risk of violence, both individually and more speculatively additively. Therefore, it is important to consider the role of CD in future studies of substance misuse and violence in schizophrenia due to its associations with both.

7.6.3 Early risk factors for violence

Early use of substances in patients with schizophrenia and pre-morbid CD is important in the risk of later violent behaviour. Substance abuse that begins very early on among people who later developed serious mental illness was associated with a greater risk of violence than substance abuse that began in adulthood (Fulwiler et al., 1997). Among those with severe mental illness, age of onset of substance abuse predicted violence after controlling for CD (Fulwiler and Ruthazer, 1999). This emphasises the importance of early onset of substance misuse in relation to later violent behaviour and hence the importance of early intervention to treat substance abuse and CD with the target of reducing the risk of future violence. Effective treatments are available for CD, particularly parenting training (Weisz et al., 2004, Scott, 2008). In addition, there are also well-established treatment programmes for adolescent substance use disorders (Hogue et al., 2014). However, co-morbid CD is known to reduce the effectiveness of substance misuse treatment programmes (Grella et al., 2001).

Understanding the early influences on the complex trajectory towards violence is crucial in order to reduce the risk of future violence. It is clear that CD increases the likelihood of cannabis use in early adolescence, which increases the risk of schizophrenia. Whilst there is an independent increase in the risk of violence associated with schizophrenia, pre-morbid CD and lifetime SUD are also associated with increases in the propensity to violence. Future prospective studies would benefit from focusing on the nature of these interactions and possible additive effects of these factors on the risk of violence in schizophrenia.

7.7 Strengths and limitations

7.7.1 Strengths

This study included data on a uniquely well-defined sample of men with schizophrenia who were drawn from a wide range of in-patient and out-patient mental health services, in order to achieve representative sampling across a wide geographical region of England, encompassing socially and ethnically diverse populations. The participants were comprehensively assessed, both in terms of their violence and their mental disorders. The use of the GRVS allowed for the careful objective quantification of the patients' lifetime propensity to violence using multiple data sources.

7.7.2 Limitations

This study is limited by its cross-sectional design, which did not allow temporal proximity of the measurement of the clinical variables and the violent behaviour. A prospective methodology will allow this type of consideration but will require both a larger sample and repeated assessments over time, acknowledging also the relative rarity of incidents of severe violence. As there were no patients in the sample who had CD but no lifetime SUD it was not possible to explore this relationship fully. This will be a useful focus for future research.

7.8 Conclusions

Pre-morbid CD increases the risk of violence in men with schizophrenia, but CD also increases the risk of lifetime SUD, which also increases the risk of violence. Hence both CD and SUD play independent roles in the propensity to violence but also interact with each other. Many previous studies of the association between substance misuse and violence in schizophrenia have not assessed CD or ASPD; as there is an association between CD and SUD this may have led to an over-estimation of the effect of SUD, with a lack of recognition of the independent role of CD. It is clear that prospective longitudinal studies are needed to explore the interactions and relationship between CD and early SUD and future violent behaviour. CD and early substance misuse may be fruitful targets for early intervention and treatment in order to reduce the risk of later violence among men with schizophrenia. In addition, treatment programmes for adult patients with schizophrenia who have been violent need to address management of SUD as well as psychosis.

Chapter 8 Structural brain abnormalities and violence in schizophrenia

8.1 Abstract

This chapter describes exploratory analyses of grey matter abnormalities associated with schizophrenia and violence. There were significant reductions in total grey matter volume and evidence of further specific reductions in grey matter volume in the left insula and left superior temporal gyrus in patients with schizophrenia compared to healthy controls. In patients with schizophrenia, lifetime propensity to violence was associated with greater grey matter in the left caudate, using two analysis methods. Across all participants, there was a negative correlation between psychopathy score and volumes of the left insula and left superior temporal gyrus.

8.2 Background

8.2.1 Structural imaging studies in schizophrenia

Schizophrenia is associated with a number of structural brain abnormalities. However, despite decades of research, that began with the earliest post-mortem examinations, to studies using the most advanced brain imaging techniques, the nature of these abnormalities, and what they tell us about the underlying pathophysiology of the disorder remains poorly understood. For example, there is considerable heterogeneity in the distribution and effect sizes of brain differences across studies (Van Erp et al., 2016). Recent meta-analyses were reviewed to obtain an overview of the current knowledge of structural brain abnormalities in schizophrenia.

Meta-analyses have demonstrated grey matter reductions in the insula, thalamus and anterior cingulate gyrus (Glahn et al., 2008, Ellison-Wright and Bullmore, 2010, Bora et al., 2011); superior temporal gyrus, medial frontal gyrus and amygdala (Bora et al., 2011, Ellison-Wright and Bullmore, 2010); hippocampus (Ellison-Wright and Bullmore, 2010) and inferior frontal gyrus (Bora et al., 2011). The largest schizophrenia brain volume meta-analysis conducted to date, that included data from over 18,000 subjects, found that patients with schizophrenia have significantly reduced intracranial and total brain volumes, with a marked reduction in total grey

matter volume and with focal grey matter reductions (Haijma et al., 2013). A recent collaborative region of interest study of 15 worldwide cohorts of patients with schizophrenia, found that patients had smaller hippocampal, amygdalar and thalamic volumes, and larger palladial and lateral ventricular volumes (Van Erp et al., 2016).

A meta-analysis of diffusion tensor imaging studies found significant abnormalities in white matter in two regions: the first region in the left frontal lobe, has white matter tracts principally linking the frontal lobes, thalamus and cingulate gyrus; and the second region in the left temporal lobe, has white matter tracts interconnecting the frontal lobe, insula, hippocampus-amygdala, temporal and occipital lobe (Ellison-Wright and Bullmore, 2009). This may indicate disruption of the white matter tracts that connect grey matter cortical and subcortical structures which are known to be abnormal in schizophrenia. Further reviews report abnormalities in multiple white matter regions, including the uncinate fasiculus, fornix, cingulum bundle, arcuate fasiculus, anterior commissure and interhemispheric fibres (Fitzsimmons et al., 2013, Yao et al., 2013, Bora et al., 2011)

Reduced grey matter volume is evident at first presentation of psychosis but further reductions are associated with longer duration of illness and higher doses of antipsychotic medication at the time of scanning (Haijma et al., 2013). Progressive volume loss in patients with schizophrenia has been demonstrated in longitudinal studies, in both cortical (Vita et al., 2015) and subcortical (van Haren et al., 2016) grey matter, but the degree, timing and anatomical specificity of any changes remain uncertain. Male gender and the presence of negative symptoms are associated with more extensive grey matter abnormalities, while a longer duration of illness is associated with greater grey and white matter deficits (Bora et al., 2011).

The causes of the structural brain abnormalities that have been demonstrated in schizophrenia are under investigation, with both genetic and environmental factors being of importance. Links between genetic liability to psychosis and brain abnormalities have been explored in studies of individuals at clinical or familial high risk of developing schizophrenia. Grey and white matter abnormalities and differences in the morphology of the cortex have been found in individuals at high risk compared to healthy controls, but to a lesser extent than in patients, suggesting that

structural abnormalities may be markers of vulnerability to schizophrenia (Bois et al., 2015). The role of genetic factors is also demonstrated by the finding that monozygotic twins concordant for schizophrenia have reduced thalamic volume compared to discordant twins with schizophrenia, whose thalamic volume is also reduced compared to healthy controls (Ettinger et al., 2007). Heritability of more widespread grey matter abnormalities, including in the insula and medial frontal and temporal lobes, has been suggested in a study of unaffected siblings (Turner et al., 2012). In addition, specific genes have been linked to structural brain abnormalities, for example, alterations in grey matter volume in the prefrontal and temporal regions have been associated with disrupted-in-schizophrenia-1 (DISC1) polymorphisms (Trost et al., 2013).

There are also numerous confounding environmental factors which can influence the volume of brain structures, including foetal hypoxia, smoking, cannabis use, and nutritional and hydration status (Van Erp et al., 2016). In recent years there has been a focus on the role of antipsychotic medication in brain abnormalities in schizophrenia. Cumulative exposure to antipsychotic treatment has been correlated with global loss of grey matter (Fusar-Poli et al., 2013), with some indication that greater grey matter loss may be associated with first generation antipsychotics compared to second generation (Vita et al., 2015). The association is complicated by several factors, including compliance (whether the patient takes the dose that is prescribed and hence reported for such studies) and the possibility that patients taking higher doses of antipsychotics have a more severe form of the illness. In addition, relapse duration has been associated with significant reductions in both global and regional brain volumes (Andreasen et al., 2013). However, effect sizes for total brain and grey matter volume reductions in samples of antipsychotic-naïve first episode of psychosis patients were approximately 75% of those in medicated patients, indicating that most of the brain volume reduction in schizophrenia is present before treatment is initiated (Haijma et al., 2013). Therefore, reduced grey matter is integral to the illness and whilst antipsychotic medication may contribute to these deficits it cannot be the sole cause.

8.2.2 Structural imaging studies in schizophrenia and violence

The literature relating specifically to imaging studies of schizophrenia and violence was reviewed in section 2.8. To recap, the structural magnetic resonance (MR) imaging studies of

violence in schizophrenia provide consistent evidence, from both region of interest and whole brain studies, of reduced grey matter volume in the hippocampus of patients with schizophrenia who are violent compared to those who are not (Barkataki et al., 2006, Yang et al., 2010, Kumari et al., 2009a, Kumari et al., 2013). There is also evidence of grey matter changes in the inferior frontal region (Hoptman and Antonius, 2011, Narayan et al., 2007, Schug et al., 2010, Hoptman et al., 2014). Some results are more inconsistent, for example one region of interest study found evidence that greater grey matter volume in the orbitofrontal region was associated with greater levels of aggression (Hoptman et al., 2005); while another region of interest study found reduced grey matter volume in the same region was linked with a history of serious violence (Kumari et al., 2009a). The reason for this inconsistency is not known but it may be of relevance that one study measured aggression using the OAS and PANSS, and one study considered an act of fatal or near fatal violence towards a victim, and so they were utilizing different definitions of aggression/violence. One region of interest study found an association between increased volume of the caudate and aggression (Hoptman et al., 2006) but this region has not been identified in whole brain studies of violence and schizophrenia. One of the most relevant confounding factors that may explain some of the variance in these studies is the effect of antipsychotic medication (Soyka, 2011).

It is recognised that the application of neuroimaging methods to help understand the origins of the link between schizophrenia and violence is in a state of relative infancy, compared to the schizophrenia field as a whole, while methodological challenges such as the heterogeneous nature of violence and its quantification remain largely unresolved (Hoptman and Antonius, 2011, Harris et al., 2013). This study represents one of the first to attempt to address some of these methodological challenges more robustly and aimed to deliver preliminary evidence of the associations between violence in schizophrenia and cerebral grey matter volume.

8.3 Hypotheses

Based on the available literature it was hypothesized that patients with schizophrenia, compared to healthy controls, will experience reductions in total grey matter volume and in a variety of frontal and temporal lobe cortical and subcortical structures, including in the insula,

thalamus, medial frontal gyrus, hippocampus, superior temporal gyrus and anterior cingulate gyrus.

In patients with schizophrenia, it was hypothesized that those with a greater propensity to violence will have reduced grey matter volume in the medial temporal lobe and inferior frontal gyrus and greater grey matter volume in the caudate.

8.4 Specific methodology

All participants were recruited to the study and assessed as described in chapter 4. Those participants who had no medical contraindication for a magnetic resonance imaging (MRI) scan and consented, and were able or permitted to travel to the magnetic resonance scanner in Northampton (Three Shires Hospital), underwent a structural MRI brain scan.

8.4.1 Data acquisition

Data were acquired at 1.5T using a Toshiba Excelart Vantage Atlas-X system with actively shielded magnetic field gradients and an active shield gradient coil. A fourteen element Atlas SPEEDER head, receive only array coil was used. T1, T2 and FLAIR structural sequences were collected; T2 and FLAIR weighted imaging in the trans-axial plane in conjunction with a T1 weighted volume scan acquired in the sagittal plane. The T1-weighted gradient echo sequence had the following parameters: repetition time = 12ms; echo time = 5ms; inversion time = 400; flip angle = 20°; 120 contiguous 1.1mm sagittal slices; field of view = 28 x 28cm; matrix size = 256 x 256mm; voxel size = 1.1mm x 1.1mm x 1.1mm.

8.4.2 Data processing

Data were processed and analysed using SPM8 (Wellcome Trust Centre for Neuroimaging) and the voxel-based morphometry VBM8 toolbox (Structural Brain Mapping Group) with default parameters. Voxel based morphometry (VBM) is a neuroimaging analysis technique performed on structural MR images to identify the effects of a given variable of interest on brain structure and involves spatially normalizing images from all participants in the study (Ashburner and Friston, 2000). It enabled investigation of significant differences in brain anatomy between

experimental groups, using statistical parametric mapping. VBM can be used to analyse differences in brain structure between groups or to identify a relationship in a group between brain structure and a given variable, such as a score on a particular task or questionnaire.

A fundamental problem with analysing brain structure across groups is that there may be substantial variations in large-scale brain anatomy that are due to natural variability rather than the effect of interest. The VBM method helps to overcome this problem by using a number of processes to register the images in the same normalized anatomical space. The process of VBM begins with segmentation; it identifies and separates the scan into one of four tissue types: grey matter, white matter, cerebrospinal fluid and other tissues (such as the skull). Segmented images for grey and white matter were summed to estimate total brain volume, which was then used as a covariate in the subsequent group analysis stage. After segmentation, the spatially normalized template is created. This template is then normalized (i.e. shifted and warped) to fit the Montreal Neurological Institute (MNI) template. The images were then smoothed using an 8mm full-width at half-maximum Gaussian kernel.

8.4.3 Statistical analyses

Parametric statistical models are assumed at each voxel, using the General Linear Model to describe the data in terms of experimental and confounding effects, and residual variability. Voxel-wise grey matter differences between patients and healthy controls were examined using independent t-tests, controlling for age, alcohol and drug use and total brain volume.

An exploratory whole brain analysis was conducted at an uncorrected threshold of $p<0.001$. For all significant comparisons, a p value of <0.05, family wise error (FWE) corrected for multiple comparison, was then applied. Reported voxel coordinates were converted from MNI coordinates into Talairach coordinates (Lacadie et al., 2008) and Brodmann areas (Yale BioImage Suite Package) to confirm their localization in grey matter. Anatomical descriptions of brain regions were obtained using Talairach Deamon (Lancaster et al., 2000). Results are reported with their original MNI coordinates as output by SPM8.

From those clusters in brain regions that differed significantly between the patients and controls, we focused on those which previous studies have linked with violence. Grey matter volumes of the identified clusters were extracted and any correlations between grey matter volume and both GRVS score and PCL:SV score were estimated using Spearman's rho rank correlation coefficient in SPSS 18. Finally in the patients only, regression models were constructed in SPM8 to identify areas across the whole brain that were predicted by lifetime violence propensity as indexed by GRVS score, while controlling for confounding effects of age, whole brain volume and drug and alcohol use.

8.5 Results

8.5.1 Demographics

Fifty-five participants underwent a structural MRI brain scan. One healthy participant was later excluded from the analyses due to the new discovery of a space-occupying lesion. They and their General Practitioner were advised of this chance finding, for further follow up. The demographic characteristics of the participants who were scanned are shown in table 8-1.

Table 8-1 Demographic characteristics of scanned participants

Variable	**Controls n=31**	**Patients n=23**	**Test statistic, significance**
Age	32.74 (9.32)	40.43 (8.30)	t=-3.14, p=0.003
IQ	111.00 (14.80)	88.61 (13.72)	t=5.67, p<0.001
Number of CD symptoms	1.00 (1.67)	2.52 (2.83)	U=478.50, p=0.022
Alcohol use disorder (n)	11	15	X^2 4.68, p=0.031
Drug use disorder (n)	5	12	X^2 7.95, p=0.005
PCL-SV score	0.29 (0.82)	5.96 (5.69)	U=638.50, p<0.001
Gunn Robertson Violence Score	0.61 (0.67)	2.39 (1.37)	U=611.00, p<0.001

Figures are mean and (standard deviation) unless otherwise stated

The patients' clinical characteristics are shown in table 8-2. Scanned patients compared to those patients who were not scanned, were older (40.43 vs 32.81 years, p=0.003), and were less likely to have misused cannabis (p=0.005). Fewer patients from secure units were scanned (p=0.05), which was due to not having the necessary community leave from the Ministry of Justice to travel to the MRI scanner. Scanned patients did not differ in terms of number of lifetime hospital admissions or total time spent in hospital and current dose of antipsychotic. Scanned patients also did not significantly differ from those who were not scanned in GRVS score or any of the other clinical variables in table 8-2.

Table 8-2 Clinical demographics of scanned patients (n=23)

Age of onset of schizophrenia (years)	24.30 (5.59)
Time since onset of schizophrenia (years)	16.17 (6.26)
Number of hospital admissions	4.39 (5.19)
Total time in hospital (years)	6.45 (5.38)
Current Positive And Negative Syndrome Scale	19.17 (6.78)
P score	16.87 (4.99)
N score	34.65 (5.52)
G score	70.70 (13.77)
Total score	
Current dose of antipsychotic in chlorpromazine equivalent (mg)	443.96 (289.70)
Current location (n)	
Community	7 (30%)
Open/locked ward	12 (52%)
Low secure unit	3 (13%)
Medium secure unit	1 (4%)
Mental Health Act status (n)	
Informal	3 (13%)
Community treatment order	3 (13%)
Civil section	5 (22%)

Forensic section	12 (52%)
Conduct disorder (n)	8 (35%)
Antisocial personality disorder (n)	8 (35%)
Psychopathy Checklist Screening Version score	5.96 (5.69)
Substance use disorders (n)	
Alcohol abuse	9 (39%)
Alcohol dependence	4 (17%)
Cannabis abuse	6 (26%)
Cannabis dependence	7 (30%)
Cocaine abuse	5 (22%)
Cocaine dependence	4 (17%)
Stimulant abuse	3 (13%)
Stimulant dependence	1 (4%)
Opioid abuse	0
Opioid dependence	4 (17%)

Figures are mean and (standard deviation) unless otherwise stated

8.5.2 Differences between patients and controls

Compared to healthy controls, patients had significantly lower total grey matter and total brain volume (see table 8-3).

Table 8-3 Comparison of brain volumes of patients and controls

Total volume (cm^3)	**Patients n=31**	**Controls n=23**	**Test statistic, significance**
Whole brain	1262.95 (109.60)	1197.87 (99.92)	U=243.00 p=0.047
Grey matter	696.91 (56.11)	663.54 (60.66)	U=234.00 p=0.032
White matter	566.04 (55.41)	534.33 (46.31)	U=256.00 p=0.079

Figures are mean and (standard deviation) unless otherwise stated

Brain regions where patients had significantly reduced grey matter compared to controls are shown in figure 8-1 and table 8-4. The findings in the left insula and left superior temporal gyrus remained statistically significant after FWE correction for multiple comparisons (see figure 8-2).

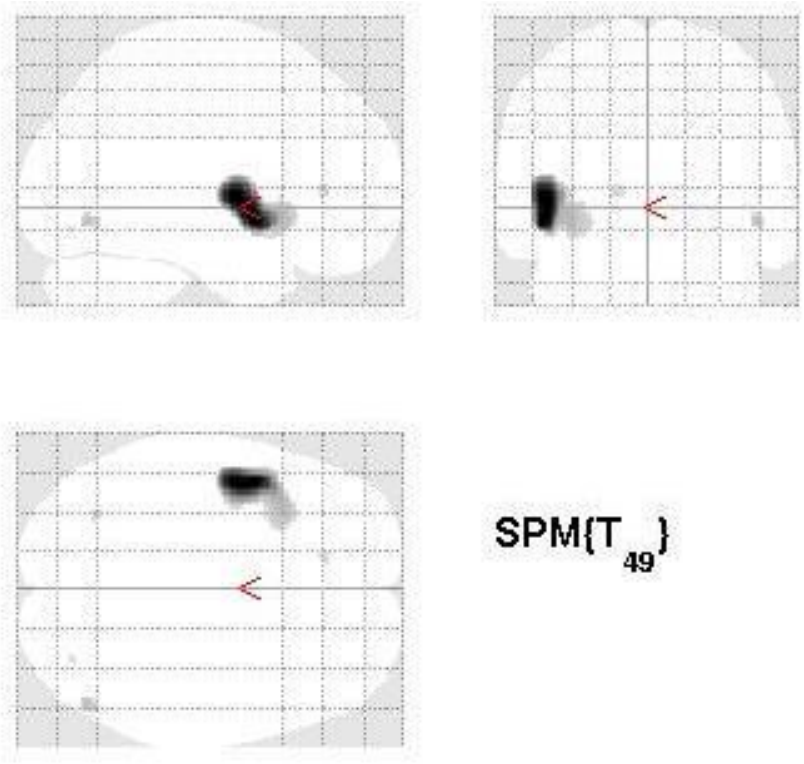

Figure 8-1 Brain regions with reduced grey matter volume in patients compared to controls (uncorrected at threshold of p<0.001)

Table 8-4 Brain regions where patients had reduced grey matter volume compared to controls (uncorrected at threshold of p<0.001)

Brain region	**BA***	**Cluster size**	**MNI coordinates**	**Z score**	**p value uncorrected**	**p value FWE corrected**
Left insula	13	1569	-45 -1 4	4.76	<0.001	0.026
Left superior temporal gyrus	22		-46 6 -5	4.72	<0.001	0.031
Right middle occipital gyrus	19	16	50 -69 -5	3.33	<0.001	0.974

Left anterior cingulate	32	11	-14 38 7	3.16	0.001	0.996
Left fusiform gyrus	19	14	-33 -64 -6	3.15	0.001	0.997

* Brodmann area

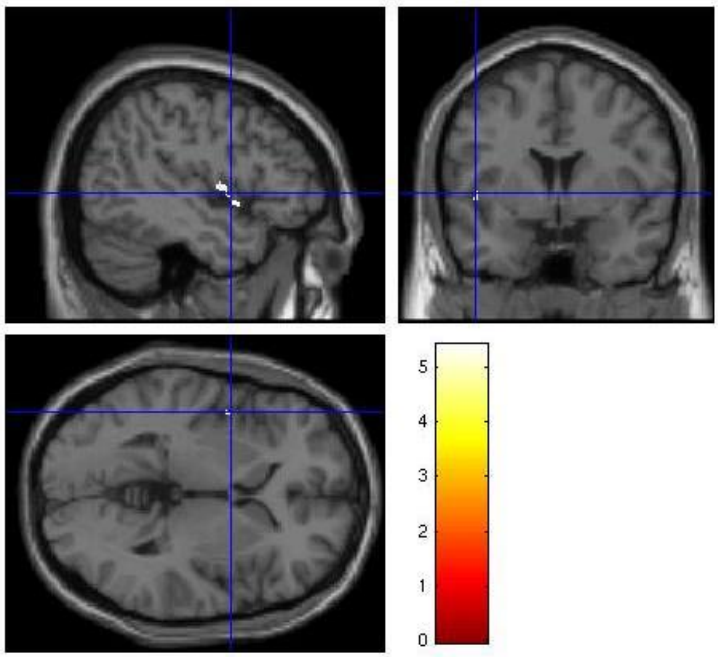

Figure 8-2 Brain regions with reduced grey matter volume in patients compared to controls that survived FWE correction

Patients had greater grey matter volume in the regions shown in table 8-5 and figure 8-3. There was one artefact where a cluster was not located in grey matter. None of these regions remained statistically significant after FWE correction.

Table 8-5 Brain regions where patients had greater grey matter volume compared to controls (uncorrected at threshold of p<0.001)

Brain region	**BA***	**Cluster size**	**MNI coordinates**	**Z score**	**p value uncorrected**	**p value FWE corrected**
Right middle temporal gyrus	20	145	56 -43 -12	3.73	<0.001	0.687
Right caudate		392	15 -19 24	3.71	<0.001	0.712
Right thalamus			2 -19 21	3.41	<0.001	0.947
Left middle temporal gyrus	21	80	-69 -42 -9	3.40	<0.001	0.952
Right caudate		44	4 0 21	3.36	<0.001	0.965
Left caudate		21	-2 12 4	3.29	<0.001	0.982
Left middle occipital gyrus	19	11	-48 -81 3	3.22	0.001	0.993
Left inferior frontal gyrus	11	13	-20 38 -21	3.16	0.001	0.996

* Brodmann area

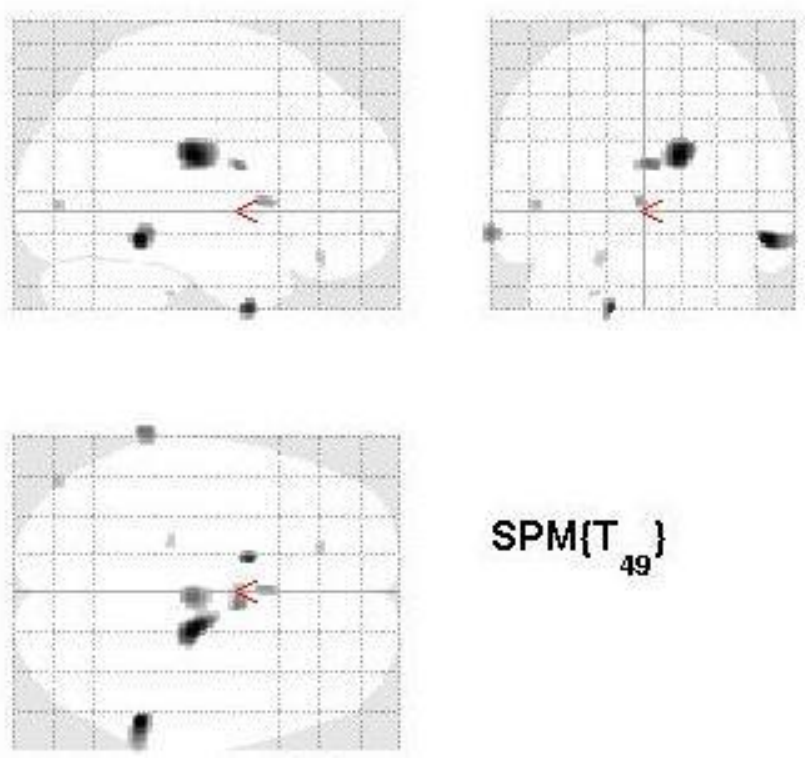

Figure 8-3 Brain regions with greater grey matter volume in patients compared to controls (uncorrected at threshold of p<0.001)

8.5.1 Grey matter volume and violence in the patient group

8.5.1.1 Correlation

Of the regions which differed significantly in grey matter volume between patients and controls, we then focused on the caudate and middle temporal gyrus as they had already been identified in the literature as linked to the risk of violence in schizophrenia. Among the patients, the volume in the right middle temporal gyrus was positively correlated with the GRVS at a trend level (r= 0.37, p=0.08). There was no association between volume in the left middle temporal gyrus and GRVS. Three cluster peaks were located in the caudate; there was a statistically significant positive correlation between the left caudate volume and GRVS score (r=0.50, p=0.01; see figure 8-4) and one in the right caudate was positively correlated with GRVS at trend level (e, r=0.39, p=0.07). Caudate volume was not correlated with either duration of illness or current antipsychotic dose.

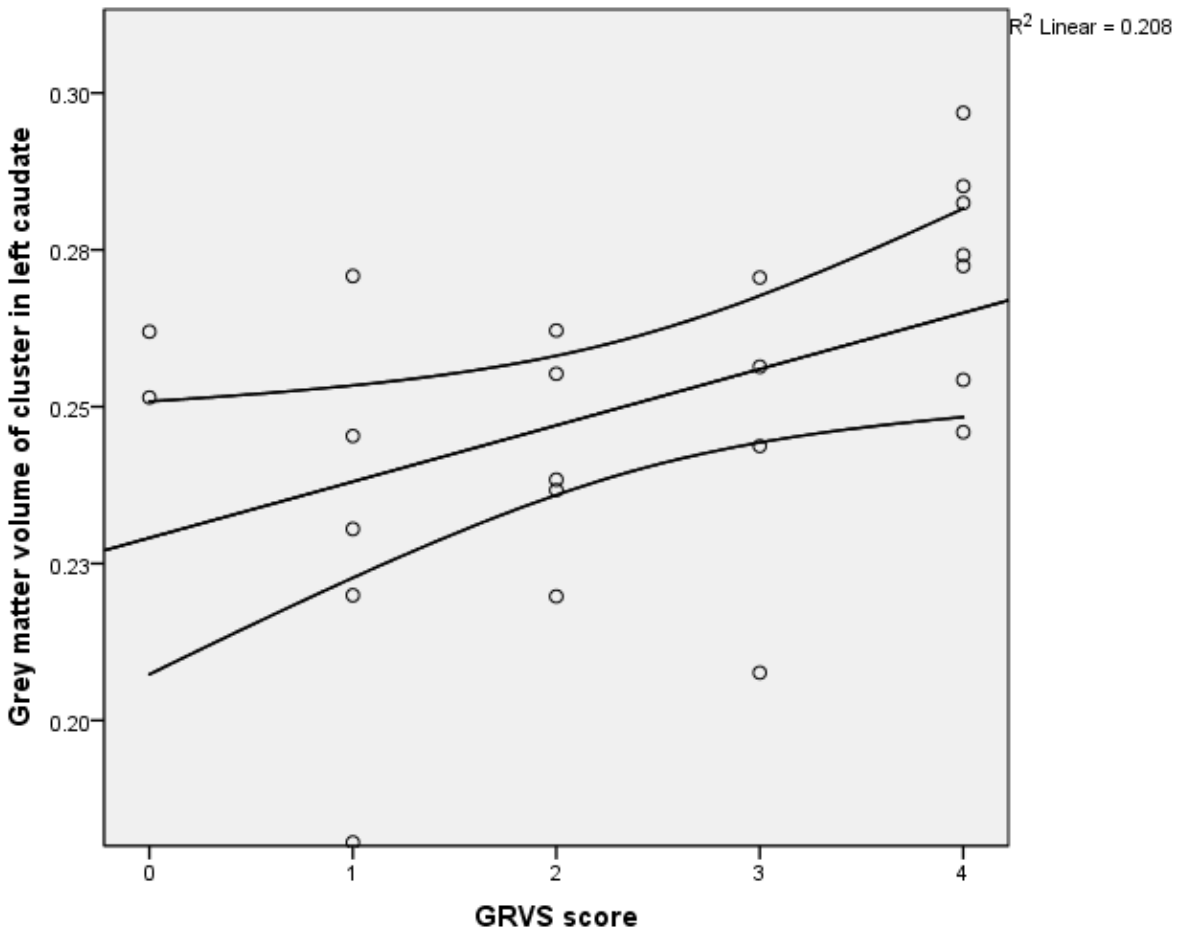

Figure 8-4 Scatter plot of grey matter volume of the cluster in left caudate (-2 12 4) and GRVS score with line of best fit and 95% confidence intervals

8.5.1.2 Regression

Regression models were constructed in SPM8 to identify areas across the whole brain that were predicted by lifetime violence propensity as indexed by GRVS score, while controlling for confounding effects of age, whole brain volume and drug and alcohol use. Those brain regions in which GRVS score predicted greater grey matter volume in the patients are shown in figures 8-5 and 8-6 and table 8-6. There was a cluster identified in the left caudate, as in the results of the correlation described above, however none of these regions remained statistically significant after FWE correction. There was one artefact where a cluster was not located in grey matter. There were no clusters where grey matter volume reduced with GRVS.

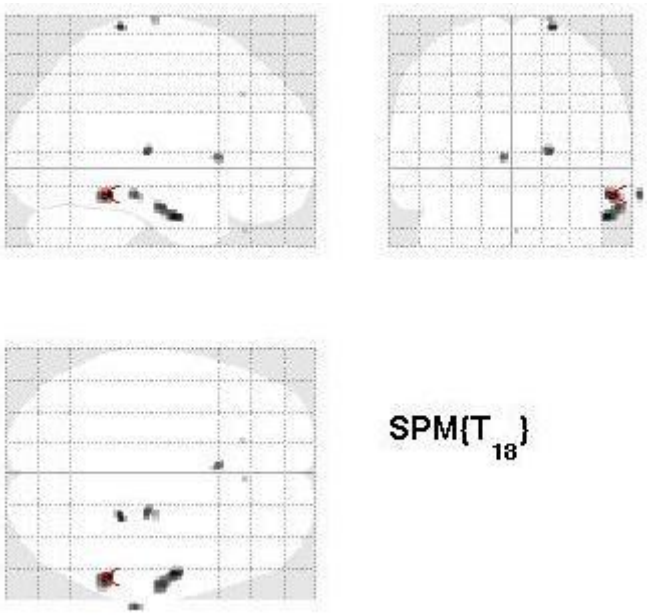

Figure 8-5 Brain regions in which GRVS score predicted greater grey matter volume (uncorrected at threshold of p<0.001)

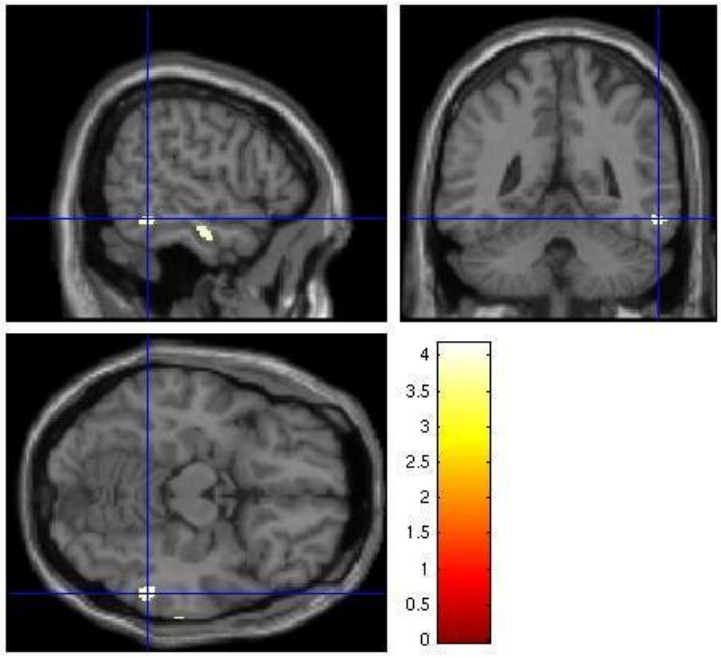

Figure 8-6 Regions in which GRVS score predicted greater grey matter volume (uncorrected at threshold of p<0.001)

Table 8-6 Brain regions in which GRVS score predicted greater grey matter volume (uncorrected at threshold of p<0.001)

Brain region	BA*	Cluster size	MNI coordinates	Z score	p value uncorrected	p value FWE corrected
Right inferior temporal gyrus	20	77	56 -45 -14	3.44	<0.001	0.976
Right inferior temporal gyrus	18	114	54 -6 -26	3.41	<0.001	0.984
Right inferior temporal gyrus	20		58 -13 -21	3.34	<0.001	0.992
Right post central gyrus	3	19	24 -36 76	3.38	<0.001	0.988
Right thalamus		11	21 -22 9	3.32	<0.001	0.994
Left caudate		17	-4 18 6	3.30	<0.001	0.995
Right pre central gyrus	6	7	21 -18 81	3.18	0.001	0.999

*Brodmann area

8.5.2 Psychopathy

Further post hoc analyses were conducted with the PCL:SV scores and the two brain regions which differed significantly between patients and controls after FWE correction (left insula and left superior temporal gyrus). Within the patients only, there was no statistically significant correlation between PCL:SV and the volume of grey matter in either region. However, when considering all scanned participants, both the left insula (r= -0.53, p<0.001) and the left superior temporal gyrus (r= -0.50, p<0.001) were negatively correlated with PCL:SV score (see figures 8-7 and 8-8).

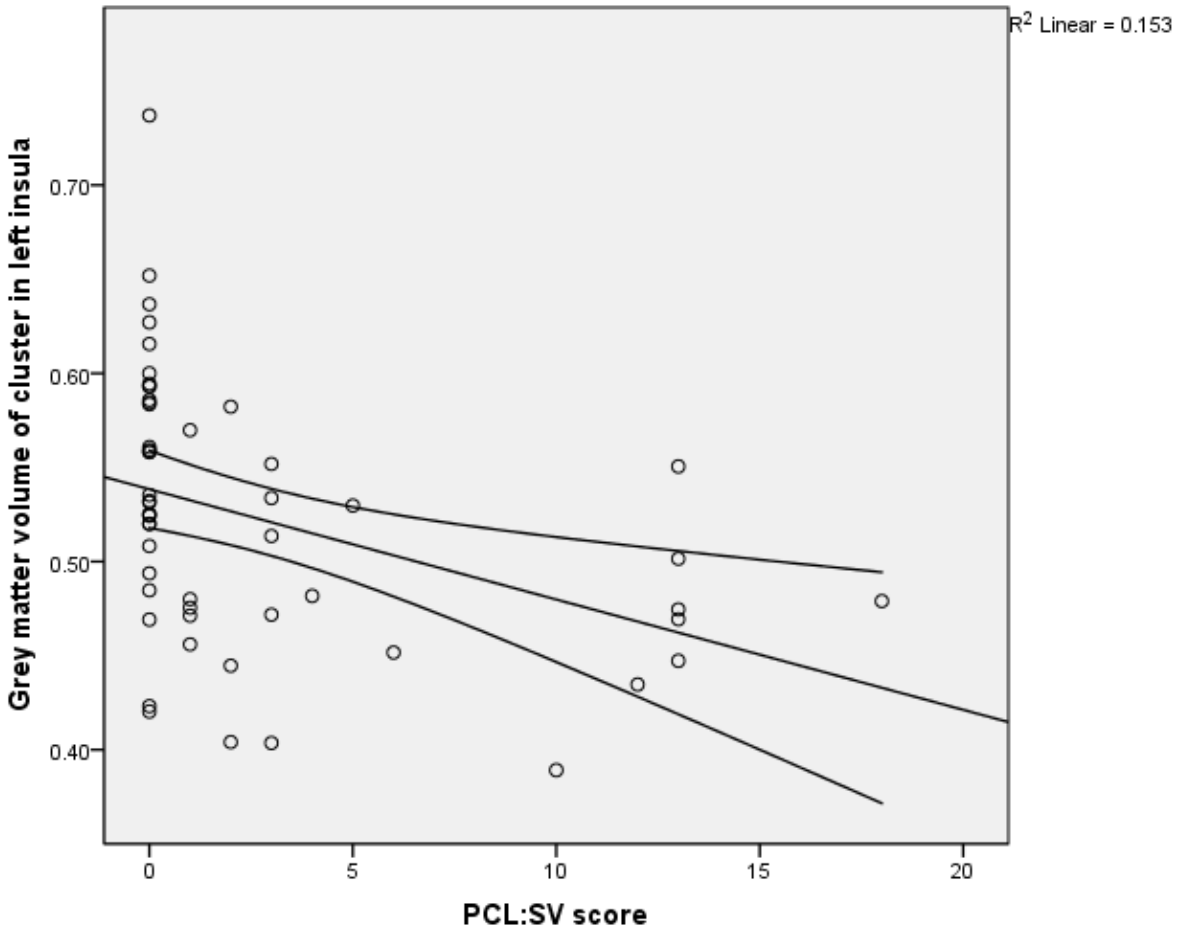

Figure 8-7 Scatter plot of grey matter volume of the cluster in the left insula (-45 -1 4) and PCL:SV score with line of best fit and 95% confidence intervals

8.6 Discussion

8.6.1 Schizophrenia

This structural MR brain imaging study found significant reductions in total grey matter volume and evidence of further specific reductions in grey matter volume in clusters in the left insula and left superior temporal gyrus in patients with schizophrenia compared to healthy controls. This was after correcting for multiple comparisons and co-varying for age, alcohol and drug use and total brain volume. While other regions, including in the left anterior cingulate and left fusiform gyrus, did differ between patients with schizophrenia and controls, these did not survive stringent FWE correction.

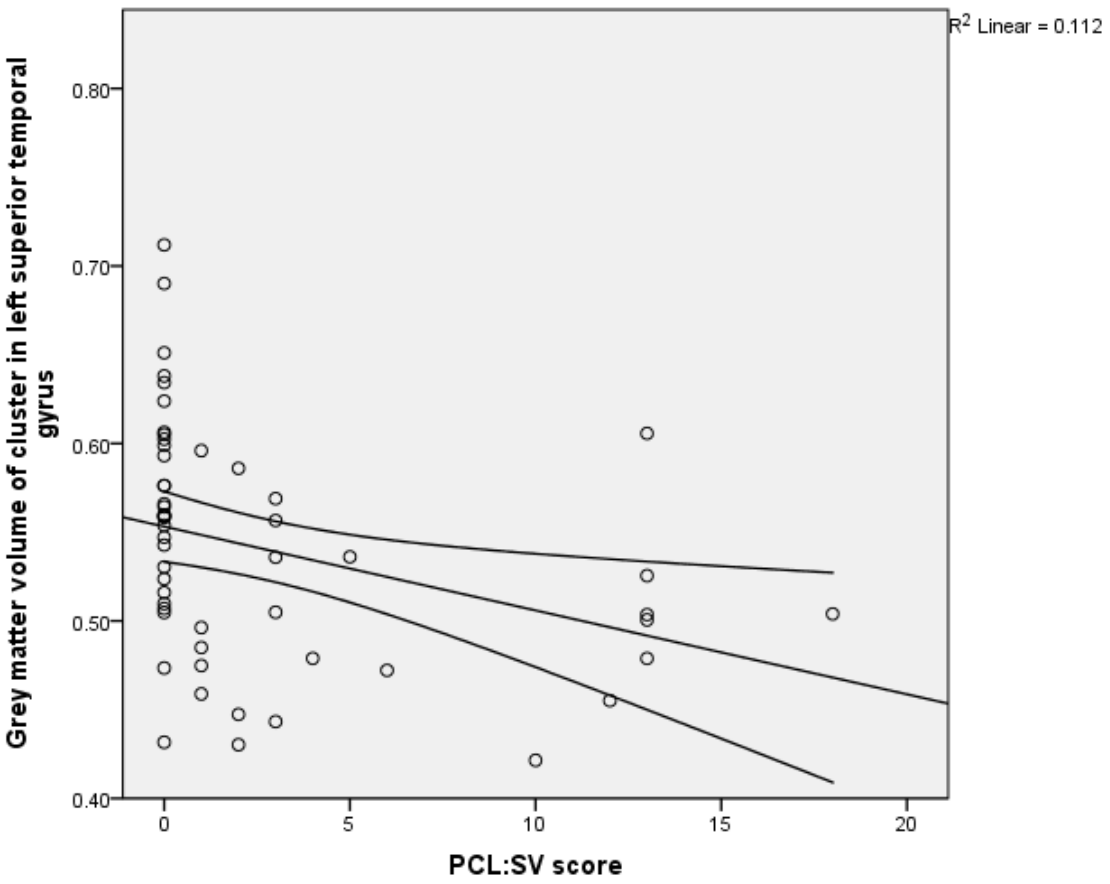

Figure 8-8 Scatter plot of grey matter volume of the left superior temporal gyrus (-46 6 -5) and PCL:SV score with line of best fit and 95% confidence intervals

8.6.1.1 Comparison with whole brain studies of schizophrenia

Grey matter volume reductions, both globally and in specific regions, are a robust finding in schizophrenia, supported by individual VBM studies (Nenadic et al., 2015, Gupta et al., 2015) and a voxel-wise, coordinate based meta-analysis of VBM studies, that identified that patients had reduced grey matter density relative to controls in a network of regions, the largest cluster centred on the left insular cortex (BA 13) and also included the STG (BA 22 and 38) (Glahn et al., 2008). Our results of reduced grey matter in the left insula (BA 13) and left STG (BA 22) were consistent with this. Other meta-analyses of VBM studies have also found grey matter deficits in the insular cortex and STG in patients with schizophrenia (Ellison-Wright et al., 2008, Ellison-Wright and Bullmore, 2010).

8.6.1.2 Comparison with region of interest studies of schizophrenia

An early review (Shenton et al., 2001), identified that the majority of imaging studies in schizophrenia reported abnormalities in the STG. The smaller bilateral STG volumes found in schizophrenia derive from both the cortical thickness and surface area but not local gyrification, and may be particularly marked in the lateral region of the gyrus (Ohi et al., 2016). In relation to the insula, a meta-analysis of region of interest studies of the insula found medium-sized reduction of insula volume in schizophrenia, of greatest magnitude in the anterior subregion (Shepherd et al., 2012).

Our results support some of our hypotheses, that there would be reduced total grey matter volume, with specific reductions in the insula and superior temporal gyrus, among patients with schizophrenia. Whilst our findings are consistent with the previous imaging literature in schizophrenia, other hypotheses that there would be reductions in grey matter in other brain regions, were not supported by our results. This particularly relates to not demonstrating reduced grey matter of the hippocampus, which is consistently found in both whole brain and region of interest studies (Chen et al., 2014, Wright et al., 2000). Indeed, the largest retrospective meta-analysis to date, which examined 38 brain structures, analysed using a variety of different methods, found the largest effect size for smaller hippocampal volumes in patients versus controls (Haijma et al., 2013). The largest effect size was also observed for smaller hippocampal volumes in a recent region of interest study of subcortical structures in more than 2000 patients with schizophrenia (Van Erp et al., 2016).

8.6.2 Violence and schizophrenia

There was a trend towards a positive correlation between GRVS score and grey matter volume of the right middle temporal gyrus. Greater grey matter volume of a cluster in the left caudate was linked with increasing GRVS score, and thus a greater propensity to violence, using two analysis methods. Firstly, a cluster in the left caudate differed significantly between patients and controls after correcting for multiple comparisons and then volumes of this cluster among patients were positively correlated with GRVS. Secondly, in the patient group, regression analyses in SPM8 also identified a cluster in the left caudate as being associated with GRVS,

after co-varying for age, alcohol and drug use and total brain volume. Together these results support our hypothesis that greater grey matter volume of the caudate is associated with an increased propensity to violence. All the results of the regression analyses were of greater, rather than reduced, grey matter being linked with violence but none of these results survived stringent FWE correction.

8.6.2.1 Comparison with whole brain studies of violence and schizophrenia

One previous study reported an association between the right middle temporal gyri and aggression in patients with schizophrenia (Lui et al., 2009), however the association was in the opposite direction to this current finding, and reported reduced grey matter volume rather than increased volume as in this study. It is not possible to determine the reason for this, and further studies will be required to confirm the direction of any association. However, there are notable differences in characteristics between the patients in the two studies, which may contribute to the differing findings; the participants in the previous study (Lui et al., 2009) were in their first episode of schizophrenia (hence were younger, with a shorter duration of illness), were antipsychotic-naïve and the measure of aggression was a current PANSS score rather than lifetime propensity to violence. Therefore, the participants in the two samples had other differences between them which are known to affect grey matter volume, and in addition a different definition and measure of aggression/violence was utilized in each study. This may limit the ability to compare the results of the two studies.

No whole brain studies were identified in which increased caudate volume was associated with violence in schizophrenia.

8.6.2.2 Comparison with region of interest studies of violence and schizophrenia

One region of interest study of violence and schizophrenia considered the caudate (Hoptman et al., 2006); finding that increased volume of the caudate was associated with greater levels of aggression measured by OAS and PANSS, after controlling for the effects of age, whole brain volume and substance use disorders, as in this study. The authors point out that long-term treatment with typical antipsychotics can increase caudate volume (and their sample was of

chronically ill patients) but they did not find a relationship between increased caudate volume and duration of illness (Hoptman et al., 2006), although there is no direct measure of exposure to antipsychotics so this confounder has not been adequately adjusted for. Similarly, in the current study, there was no correlation between caudate volume and either duration of illness or dose of antipsychotic (although this is only current prescription and does not take account of length of time of treatment).

No region of interest study of violence and schizophrenia was identified which has examined the middle temporal gyri. The relevant whole brain study is described in section 8.6.2.1 above.

8.6.3 Psychopathy

Across all scanned participants, there was a negative correlation between PCL:SV score and volumes of the left insula and left STG. This association was not present in the patient group only.

8.6.3.1 Comparison with whole brain studies of psychopathy

A meta-analysis of imaging findings in antisocial, violent and psychopathic individuals found reduced prefrontal structure and function in antisocial individuals, which were localized to the right orbitofrontal cortex, right anterior cingulate and left dorsolateral prefrontal cortex (Yang and Raine, 2009). A further review suggested that psychopathy specifically may be most associated with grey matter volume loss in the amygdala, hippocampus and STG (Dolan, 2010). A VBM study found significant grey matter reductions in the right STG in men with psychopathy (Müller et al., 2008). Indeed it has been suggested that abnormalities in the STG are a key discriminator between individuals with psychopathy and healthy controls (Sato et al., 2011). This is consistent with our finding that reduced grey matter in the left STG was associated with increased PCL:SV score.

Grey matter reductions in the insula have been found in patients with high psychopathy scores, and the degree of structural abnormalities were significantly related to the interpersonal/affective dimension of psychopathy (de Oliveira-Souza et al., 2008). There is

some evidence of a functional abnormality of the insula, as offenders with psychopathy have been shown to have increased activation in the anterior insula in response to punished errors in an event-related probabilistic response reversal task, in contrast to controls, which is thought to indicate altered organization of the information-processing system responsible for reinforcement learning (Gregory et al., 2015). The insula is centrally associated with cognitive-affective processing and disruption of this processing may have a role in behaviours such as rule-breaking that are seen in psychopathy (Raine and Yang, 2006). Therefore there is some support in the literature for abnormalities in the insula being associated with psychopathy as has been demonstrated in our study. The abnormalities in the insula and STG are likely to be part of a distributed fronto-temporal network of grey matter abnormalities in psychopathy.

8.6.3.2 Comparison with region of interest studies of psychopathy

A region of interest analysis within a VBM study, revealed no significant differences in the STG or anterior insula between participants with ASPD with and without psychopathy (Gregory et al., 2012). The majority of region of interest studies in psychopathy have focused on the prefrontal cortex and amygdala, due to these regions being considered to be associated with the instrumental violence that occurs in psychopathy. One region of interest study of the amygdala, showed that individuals with psychopathy had significant bilateral volume reductions in the amygdala compared with healthy controls (Yang et al., 2009). This finding was not replicated in a subsequent VBM study, although it found reduced grey matter volumes in the prefrontal cortex (Gregory et al., 2012). It has been suggested that future region of interest studies in psychopathy could usefully focus on regions such as the insula, in addition to the prefrontal cortex (Yang and Raine, 2009).

8.6.4 Caudate and violence in schizophrenia

In this study of men with schizophrenia, lifetime propensity to violence was associated with greater grey matter in the left caudate, using two analysis methods. One previous study in patients with schizophrenia found larger caudate volumes were associated with greater levels of aggression (Hoptman et al., 2006). However, this was not supported by another study, where

caudate volume did not differ between healthy controls, participants with ASPD, and patients with schizophrenia with and without a history of serious violence (Barkataki et al., 2006).

The caudate is one of the structures that constitute the striatum and has a role in a range of motor and non-motor functions, including as part of the reward system. It has been suggested that caudate dysfunction may interfere with the normal functioning of the frontal-subcortical circuitry and hence contribute towards aggression (Hoptman et al., 2006). In addition to structural imaging data, there is preliminary evidence from functional imaging that caudate dysfunction may contribute to violent behaviour in schizophrenia. Patients with schizophrenia and a history of serious violence showed impaired performance in a response inhibition task and reduced activity in the caudate in the condition requiring inhibition (Barkataki et al., 2008). The caudate is also implicated in prepulse inhibition of the startle response, which is a measure of automatic inhibition and reduced prepulse inhibition has been found to have a modest association with violence in schizophrenia (Kumari et al., 2005).

There is also relevant evidence regarding the role of the caudate in violent behaviour in individuals with psychopathy. Greater total grey matter volume has been found in the striatum of men with psychopathy and grey matter volume in the caudate head specifically was associated with impulsivity and sensation seeking features of psychopathy and caudate body volumes were primarily associated with the interpersonal and affective features (Glenn et al., 2010). The authors speculated that increased volume of the caudate body may reflect an enhanced ability to deceive others and the head of the caudate may be involved in responding to rewarding feedback (Glenn et al., 2010). Compared with non-offenders, violent offenders (without schizophrenia) presented with a larger grey matter volume in the right caudate head, and these changes were positively correlated with PCL:SV scores and Life History of Aggression scores (Schiffer et al., 2011). The authors suggested that this may be related to a specific deficit among psychopaths in stimulus-reinforcement learning, such that they rely, almost exclusively, on reward and fail to take account of punishment (Schiffer et al., 2011). A subsequent study found that among psychopaths compared to healthy controls, there was no difference in the volume of the caudate but there were morphological changes which were negatively correlated with the lifestyle factor of the PCL-R (Boccardi et al., 2013).

Treatment with both first (Chakos et al., 1994) and second generation (Okugawa et al., 2007) antipsychotics has been shown to increase caudate volumes. It is a potential confounding factor that patients who are presenting with violent behaviour may be treated with large doses of antipsychotics. Therefore it may be that caudate volume increase is a consequence of antipsychotic drug use rather than being an antecedent of aggression (Hoptman et al., 2006). However, clozapine treatment led to caudate volume reduction in three studies, with one study demonstrating a 10% volume reduction after one year of taking clozapine (Mouchlianitis et al., 2016). It may be of relevance to our findings about violence and the caudate, that clozapine has specific anti-aggressive effects in patients with schizophrenia (Frogley et al., 2012). It is possible that caudate dysfunction, whether its origin is pharmacological or otherwise, is of relevance in violent behaviour in schizophrenia. Therefore, the caudate may be a focus for future imaging studies of violence in schizophrenia, taking account of the additional role of psychopathy and antipsychotic treatment as a confounding factor, which was not possible in the current study due to sample size.

8.7 Strengths and limitations

8.7.1 Strengths

This study included data on a well-defined clinical sample of men with schizophrenia who were drawn from a wide range of in-patient and out-patient clinical services. The participants were comprehensively assessed, both in terms of their background history, generally and as it related to violence, and their mental disorders. The presence of the MRI scanner on one of the hospital sites where patients were recruited, allowed some restricted patients to be scanned for this study, which would not have been possible if the MRI scanner was at a different hospital site.

The use of the GRVS allowed for the objective quantification of the patients' lifetime propensity to violence. The previous imaging studies of violence in schizophrenia, have utilized a group comparison of violent and non-violent participants, which does not account for the heterogeneity of violence. Use of the GRVS has allowed exploration of correlations across a scale of propensity to lifetime violence, rather than a dichotomous presence or absence of violence.

Some potential confounders were considered as the analyses controlled for age, total brain volume and alcohol and drug use disorders.

8.7.2 Limitations

Images were acquired on a clinical Toshiba scanner that was not fully optimised for central nervous system imaging. Due to the field of view some participants' data contained an artefact in the lateral temporal lobes, which compromised image quality in that region. Noise in the data led to less than optimal grey/white contrast and prevented a region of interest analysis of small medial temporal lobe structures. As with all VBM studies, the precision of identifying brain regions is limited by the precision of the processing steps and for example the later transformation from MNI to Talairach coordinates and potential disparity between results.

The relatively modest sample size for this difficult to recruit sample may have resulted in a lack of power to detect significant results and a failure to reject a false null hypothesis (type II error). In addition, as anticipated the patients had multiple co-morbidities (e.g. antisocial personality disorder and substance use disorders), which may have influenced the result, although substances use disorders were controlled for in the analysis. As discussed above, antipsychotic use is associated with reductions in total grey matter but also specifically increase in caudate volume, and so this may also have contributed to the results. Although information was obtained during data collection about such variables, it was not possible to account for them all in the analyses due to the limits of the sample size and statistical power.

8.8 Conclusions

This chapter describes exploratory analyses of structural brain abnormalities associated with schizophrenia and violence. The primary finding is of greater grey matter of the left caudate being associated with increased lifetime propensity to violence. This is consistent with one previous study of individuals with schizophrenia and several of individuals with psychopathy. Imaging studies of violence in schizophrenia is a developing area of research and further work is needed to elucidate these associations more clearly.

Chapter 9 Discussion

9.1 Abstract

In this chapter the results of the different components of this study are summarized. They are placed in the context of the existing literature and concepts drawn together into a hypothetical model of violence in schizophrenia. Conduct disorder, substance use disorders, childhood adversity, schizophrenia and violence are all associated with each other. Hence there is a complex interplay of factors, with their origin in childhood, which increase the risk of violent behaviour in schizophrenia. Future directions for research in the field are suggested.

9.2 Background

Violence is a complicated behavioural expression that has multiple causes, which may be of increased or decreased relevance, both between individuals and at differing times in an individual's lifetime. It is not achievable to identify a certain factor that causes violence but rather that different factors increase the chance that someone will be violent. The most challenging aspect is developing an understanding of the complex interactions between these factors, for example whether there is a cumulative effect on violence. Specifically, in relation to schizophrenia, not just the heterogeneous nature of violence itself, but also of psychosis, has been a barrier to effective research in the field (Douglas et al., 2009).

9.3 Novelty of study

9.3.1 Pre-morbid conduct disorder

It has been suggested that violence among patients with schizophrenia may follow at least two distinct pathways, one associated with premorbid conditions, including CD, and another linked with the acute psychotic symptoms of schizophrenia (Volavka, 2014, Bo et al., 2011, Volavka and Citrome, 2011, Hodgins et al., 2014). The pathway linked with premorbid conditions is associated with higher rates of substance use disorders and higher psychopathy scores in adulthood (Tengstrom et al., 2001, Van Dongen et al., 2014); whereas in the other pathway violence is primarily linked to positive psychotic symptoms rather than antisocial traits (Van Dongen et al., 2015). Therefore, in an attempt to develop new evidence to help our

understanding of the nature of violence in schizophrenia I chose to differentiate between patterns of violent behavior in schizophrenia, and in this study specifically grouped patients on the basis of pre-morbid conduct disorder. This allowed for a more detailed of examination of this potential pathway to violence to be conducted.

9.3.2 Quantification of violence

We first conducted a systematic review relating to the measurement, rating and quantification of violent behaviour in mentally disordered populations. We identified nine tools designed to assess violence and critically evaluated them. Broadly, measurement tools tended to focus on multiple, but different, facets of violence, which included: severity of act, severity of outcome, frequency and intent, with each suggested as a valid outcome measure for violent acts. The consideration of multiple facets of violence and use of multiple sources of collateral information to inform assessment appears to provide detail; however, that detail is then often diluted as a result of categorization of sample groups into violent, or aggressive, or not violent, for example. Whilst this is beneficial in terms of sample size and study power it does not allow for consideration of all the facets of violence, such as severity, outcome and frequency. Therefore, we decided to utilize a scale to measure violence for this study to try to capture some of the detail regarding the different facets of violence that is omitted by the use of two or three categories and work towards capturing the spectrum of violence. The GRVS was selected on the basis of three primary strengths: firstly, it incorporates data on both criminal justice interventions as well as self-reported violent incidents that remain undetected by the police or courts; secondly, that it considers severity, frequency and impact of violence; and finally, that it is a scale with five categories of violence to allow more detailed grouping of the participants on the basis of their violent behaviour. The use of the GRVS in this study allowed incorporation of multiple facets of a person's propensity to violence into a quantitative summary.

9.4 Limitations

This study is limited by its cross-sectional design, which does not allow temporal proximity between the measurement of the clinical variables and the violent behaviour. A prospective methodology would allow this type of consideration but would require both a much larger

sample and repeated assessments over a long follow-up period, due to the relative rarity of incidents of severe violence.

Unfortunately, despite attempting to recruit patients from more NHS Trusts than originally planned, the patient sample size did not reach the target of 60 determined by the power calculation. This was due to some difficulties engaging Responsible Clinicians in referring potential participants for the research and the reluctance of some of the patients identified to take part. The relatively modest sample size for this difficult to recruit sample may have resulted in a lack of power to detect significant results and a failure to reject a false null hypothesis (type II error). This means that potentially clinically significant results were not detected as statistically significant due to a lack of power caused by a smaller sample size. Although many associations were detected as significant results in this study, the implication of a lack of power is that other associations with smaller effect sizes may not have been identified.

9.5 Summary of findings

9.5.1 Violence, aggressive attitudes and conduct disorder

This study has demonstrated that the GRVS has good construct validity and reasonable concurrent validity. CD, ASPD and PCL:SV score are all associated with lifetime GRVS after controlling for substance use disorders. Those patients with pre-morbid CD more frequently engaged in all types of violent behaviour, apart from choking. Aggressive attitudes measured by the BPAQ, were not associated with violence after relevant adjustments, either in all participants or the patient group only. However, pre-morbid CD was associated with aggressive attitudes in adulthood, apart from the hostility sub-scale which was associated with psychotic symptoms. Instrumental violence was associated with higher psychopathy scores. These findings lead to the conclusion that pre-morbid CD is a significant factor determining later propensity to violence or a significant marker of that later adult propensity.

9.5.2 Childhood adversity

In this study of men with schizophrenia, 94% of the most violent patients had experienced at least one form of childhood adversity. Exposure to domestic violence during childhood was

associated with violent behaviour in adulthood. As far as we are aware, this is the first time this finding has been demonstrated among individuals with schizophrenia. The cumulative number of childhood adversities was associated with adult propensity to violence and attenuation of this association suggested that CD may be a mediator of the relationship. In other words, that childhood adversity via conduct disorder may be a pathway to violent behaviour in schizophrenia.

9.5.3 Substance use disorders

This study has shown that patients with pre-morbid CD had higher rates of lifetime SUD and began using alcohol and cannabis earlier and more frequently and used a wider variety of drugs. A lifetime history of SUD was associated with an increased propensity to violence. A trend remained between SUD and violence when we considered only the group of patients who did not have pre-morbid CD, emphasising the importance of SUD in violence even in the absence of CD. In addition, CD was associated with an increased propensity to violence, after adjusting for SUD. These findings confirm that both CD and SUD are independently associated with an increased risk of violence in schizophrenia.

9.5.4 Structural imaging

This study found significant reductions in grey matter volume in the left insula and left superior temporal gyrus in patients with schizophrenia, compared to controls. The primary finding relating to violence propensity in schizophrenia was an increase in grey matter volume in the caudate that was correlated with increased lifetime propensity to violence. In all scanned participants, there was a negative correlation between psychopathy score and volumes of the left insula and left superior temporal gyrus. Caudate abnormalities have previously been implicated in violent behaviour in both schizophrenia and psychopathy.

9.6 Discussion of findings

The interactions between the variables investigated in this study, on the basis of these results and the existing literature, are shown in figure 9-1. The arrows represent the direction of the associations demonstrated but do not imply causality.

Conduct disorder is over-represented in patients with schizophrenia (Kim-Cohen et al., 2003, Hodgins et al., 2008) and has been described as a precursor to schizophrenia in some patients, with the suggestion that there are specific neurobiological mechanisms underlying this type of illness (Schiffer et al., 2013). As shown in chapter 5, premorbid CD in schizophrenia is associated with an increased propensity to lifetime violence, which is in keeping with the previous literature (Arseneault et al., 2000, Tengström et al., 2004, Hodgins et al., 2005, Swanson et al., 2008).

Childhood adversity increases the risk of CD (Afifi et al., 2011, Foley et al., 2004, Kessler et al., 1997) and exposure to interpersonal violence in childhood is associated with an increased risk of substance abuse (Cerda et al., 2012). In chapter 6, a cumulative effect of childhood adversities on lifetime propensity for violence in schizophrenia was found, which is in keeping with another study (Bosqui et al., 2014). Importantly our study has developed this further by suggesting that CD may mediate this association between cumulative childhood adversity and violence, which is consistent with a recent study in those with severe mental illness which found that childhood onset ASPD mediated the relationship between childhood trauma and recent violent acts (Bruce and Laporte, 2015). A later population survey of young men found that witnessing domestic violence in childhood was the childhood adversity most strongly associated with violence in adulthood, with psychotic symptoms and ASPD as partial mediators (González et al., 2016). It is possible that exposure to violence within the family home at an early age either validates the use of violence or desensitizes the individual to the use of violence.

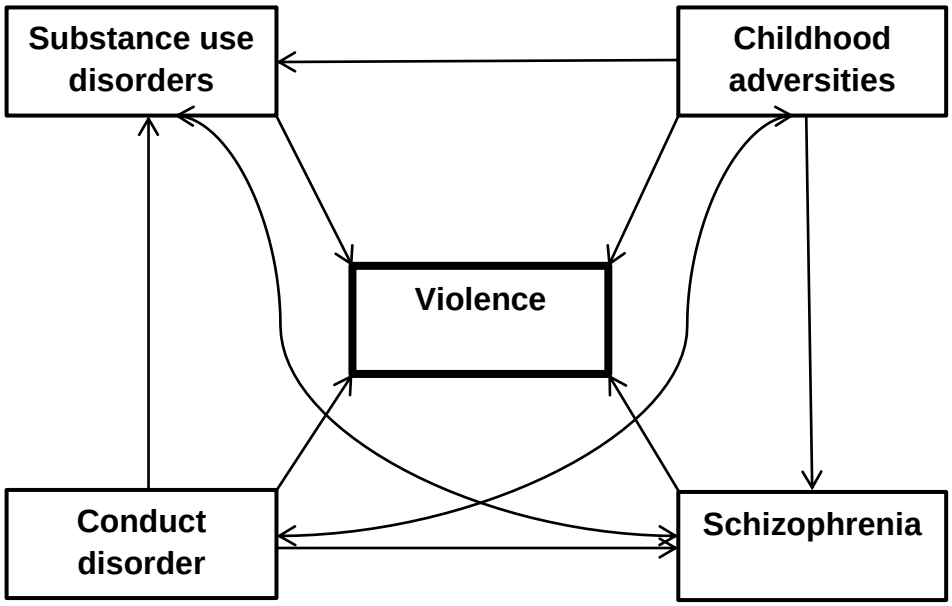

Figure 9-1 Associations between variables under investigation

Co-morbid substance misuse increases the risk of violence in schizophrenia (Swanson et al., 2006, Elbogen and Johnson, 2009, Fazel et al., 2009). In chapter 7, I showed that patients with schizophrenia and pre-morbid CD began using alcohol and cannabis at an earlier age and with greater frequency than those without pre-morbid CD. This is in line with evidence that among patients with a first episode of psychosis, the number of CD symptoms is linked to exposure to cannabis at a younger age (Malcolm et al., 2011). Patients with pre-morbid CD in this study also had an increased rate of lifetime SUD, which is supported by results of a previous study (Mueser et al., 2006).

Cannabis use increases the risk of subsequent development of psychotic symptoms and disorders, with the frequency and quantity of cannabis use influencing the strength of that association (Zammit et al., 2002, Arseneault et al., 2004, Di Forti et al., 2015). Cannabis use in early compared to late adolescence is more strongly associated with experiencing symptoms of schizophrenia in adulthood (Arseneault et al., 2002). It may be that CD symptoms independently increase the likelihood of cannabis use, which in turn increases the risk of

psychosis (Malcolm et al., 2011). Childhood adversity is also strongly associated with an increased risk for psychosis and could have a significant aetiological role (Varese et al., 2012).

Therefore, as summarized in figure 9-1, CD, SUD, childhood adversity, schizophrenia and violence are all associated with each other. Hence there is a complex interplay of factors, with their origin in childhood, which increase the risk of violent behaviour in schizophrenia. Future studies should attempt to dissect the temporality and inter-relationships of these associations.

9.7 Hypothetical pathway to violence in schizophrenia

Both CD (Blair et al., 2014) and schizophrenia (Murray and Lewis, 1988) are neurodevelopmental disorders, where a combination of genetic and environmental factors interact to modify the normal trajectory of brain development and behaviour. From an aetiological perspective one possible explanation for why CD is more common among people with schizophrenia than the general population, is that a proportion of genetic and environmental factors that influence the risk of developing each disorder are common between them.

It will be crucial for those attempting to understand the pathway from childhood vulnerability to later violence among men with schizophrenia to adopt a developmental lifetime perspective. One potential pathway may be that childhood adversity increases the risk of CD, which then increases the risk of substance misuse (Malcolm et al., 2011), perhaps earlier than in the general population, and at a more critically sensitive point in the brain's development, which then increases the risk of schizophrenia (Di Forti et al., 2015) and behaving violently (Witt et al., 2013). One hypothetical pathway to violence in schizophrenia is shown in figure 9-2.

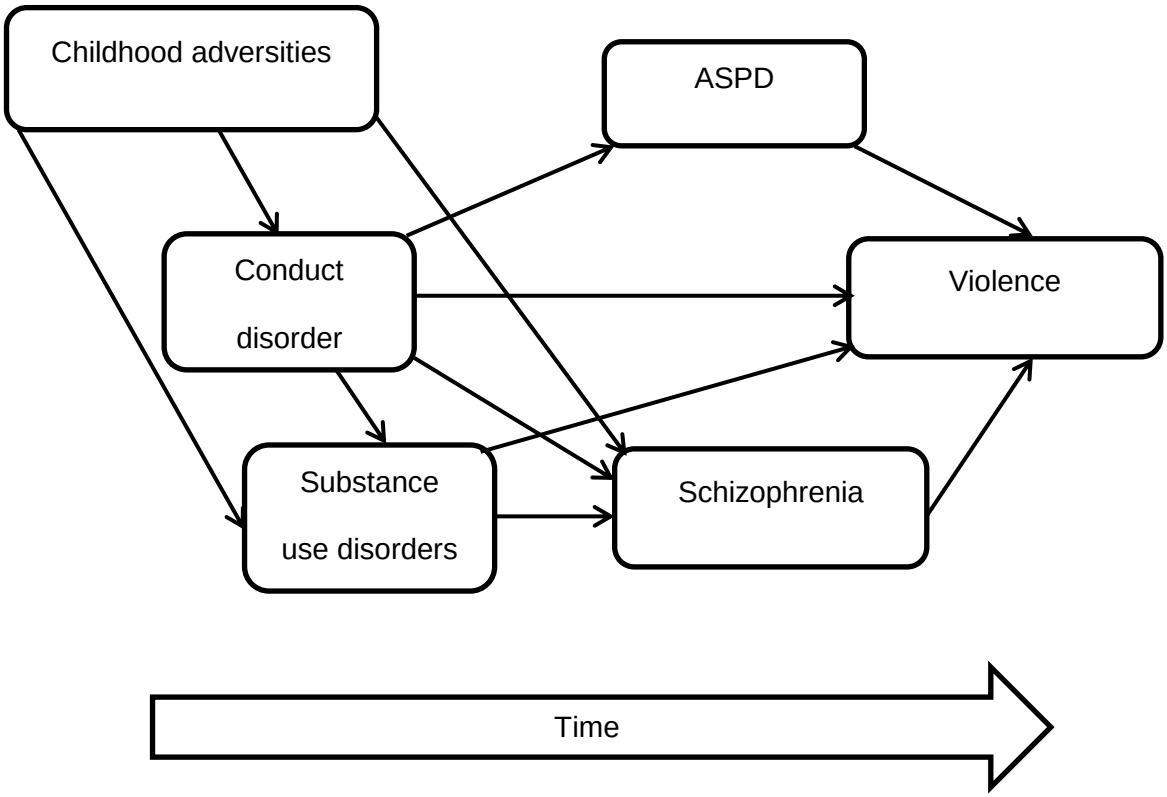

Figure 9-2 Hypothetical pathway to violence in schizophrenia

Whilst figure 9-2 conveys some of the potential interplay between factors that may contribute to the risk of violence in schizophrenia, questions remain regarding any illness-specific factors that are associated with violence. Various neuropsychological factors have been reported to be associated with violence in schizophrenia, most prominently executive dysfunction (Weiss, 2012, Harris, 2014). The existing literature on positive psychotic symptoms and associated affect, genetics and imaging, and how they may relate to the above model are discussed.

9.7.1 Positive psychotic symptoms

As discussed in chapter 2, positive psychotic symptoms have been a research focus for the drivers of the association between schizophrenia and violence. There is now an emerging literature that explores the importance of the emotional reactions to psychotic symptoms as possible drivers of aggressive behaviour in schizophrenia. Command hallucinations to harm others are associated with violence (McNiel et al., 2000) and it has been shown that anger and impulsivity are important in predicting compliance with command hallucinations to do harm

(Bucci et al., 2013). Distress (van Dongen et al., 2012) or anger (Coid et al., 2013, Ullrich et al., 2014) due to the delusional belief have been identified as a key factor explaining the link between delusions and violence. Therefore, there are indicators that anger or distress in response to positive psychotic symptoms may be important in whether these symptoms are associated with violent behaviour.

Whilst psychotic symptoms were not the focus of the current study, understanding these illness-specific factors will be a crucial component of developing our understanding of the hypothetical model outlined above. It has been suggested that there are at least two distinct pathways to violence among patients with schizophrenia, one associated with CD and another with acute psychotic symptoms (Volavka, 2014, Bo et al., 2011, Volavka and Citrome, 2011, Hodgins et al., 2014). However, it could be hypothesized that CD and ASPD may increase the likelihood of feeling anger in response to positive psychotic symptoms, hence this may be an important component of the model. It would be valuable to consider pre-morbid CD in future studies considering emotional responses to psychotic symptoms and the association with violence.

9.7.2 Genetics

There is an expanding knowledge of the biological correlates of violence in schizophrenia, with evidence from meta-analyses of the Met allele of the COMT gene conferring a significantly increased risk for violent behaviour in men with schizophrenia (Bhakta et al., 2012, Singh et al., 2012). COMT may have a more complex role in this model of violence due to its influence on other relevant factors. There is some evidence that Val carriers of the COMT gene who are exposed to childhood trauma are at greater risk of psychotic experiences (Ramsay, 2013) and perhaps more vulnerable to the psychosis-inducing effects of cannabis (Alemany et al., 2014). Also, in children with attention-deficit hyperactivity disorder, the high-activity COMT genotype is associated with antisocial behaviour measured using CD symptoms (Langley et al., 2010). Therefore, the COMT gene may have complex interactions with the response to childhood adversity, cannabis use, risk of psychotic symptoms and antisocial behaviour. Hence it may act at multiple stages of the hypothetical pathway to violence in schizophrenia.

9.7.3 Imaging

There is consistent evidence of reduced grey matter volume in the hippocampus of patients with schizophrenia who are violent compared to those who are not (Barkataki et al., 2006, Yang et al., 2010, Kumari et al., 2009a, Kumari et al., 2013). There is also evidence of grey matter changes in the inferior frontal region (Hoptman and Antonius, 2011, Narayan et al., 2007, Schug et al., 2010, Hoptman et al., 2014). Greater grey matter of the caudate predicted increased propensity to violence in this study and caudate abnormalities have previously been implicated in violence in patients with schizophrenia and with psychopathy (Barkataki et al., 2008, Glenn et al., 2010, Boccardi et al., 2013). It has been suggested that caudate dysfunction may contribute towards violence by interfering with the normal functioning of the frontal-subcortical circuitry (Hoptman et al., 2006). Therefore, in the hypothetical model of violence in schizophrenia described above, it may be that caudate dysfunction is important for all those with schizophrenia, but increasingly so if they have co-morbid psychopathy.

There is increasing evidence in the imaging literature of abnormalities in the amygdala, striatum and pre-frontal cortex in ASPD, and also in youths with antisocial behaviour or psychopathic traits, giving weight to the argument that ASPD is a neurodevelopmental condition (Raine, 2018). Whilst there is emerging evidence regarding the brain regions affected in psychopathy, ASPD, schizophrenia and specifically violence in schizophrenia, the complexities of their interactions over time, and between co-morbid disorders, will require exploration in future studies to elucidate the impact on this model.

9.8 Contributions to knowledge

There are several key contributions of this study to knowledge in the field. Firstly, I have demonstrated that the GRVS is a valid means of quantifying violence in studies of mental disorder. This can improve the richness of future data by considering different facets of violence on a spectrum and enhance the potential for analyses. The accurate definition and measurement of violence has been highlighted as an important methodological challenge in the field (Lamsma and Harte, 2015) and I propose that use of the GRVS addresses some of the issues identified by previous researchers.

The importance of pre-morbid CD as a determinant of later violent behaviour in schizophrenia has been demonstrated throughout this thesis. Patients with schizophrenia and prior CD had an increased propensity to lifetime violence compared to those without a history of CD. Pre-morbid CD was also shown to be associated with earlier and more frequent alcohol and cannabis use, increased lifetime substance use disorders and cumulative exposure to childhood adversities, all of which are themselves associated with violence.

As far as I am aware, this is the first study to demonstrate that exposure to domestic violence in childhood is associated with violence in adulthood in men with schizophrenia. In addition, the cumulative number of childhood adversities was associated with adult propensity to violence and attenuation of this association suggested that CD may be a mediator of the relationship. This potential mediation by CD is an important aspect of further understanding the role of CD in violent behaviour in schizophrenia.

The imaging component of this investigation was exploratory in nature and with a smaller number of participants than the rest of the study. Nevertheless, interesting results have emerged, particularly in relation to greater grey matter in the caudate being associated with an increased propensity to violence.

9.9 Clinical implications

9.9.1 Assessment

The findings of this study have important implications for clinicians working with men with schizophrenia. It is crucial for clinicians to understand the importance of pre-morbid CD in schizophrenia and the developmental pathway to violence. In order to assist in determining those patients who are at higher risk of behaving violently, it is of paramount importance to conduct a thorough assessment of childhood factors when they first present to mental health services. Clinicians should be assessing for pre-morbid CD and taking a careful history of a full range of childhood adversities, including exposure to domestic violence. There should also be an assessment of substance misuse in adolescence, in addition to any current substance use

disorders. Whilst psychopathy is robustly associated with violence, this is a lengthy assessment to undertake which requires specialist training to administer, therefore assessment of pre-morbid CD is a more practical and hence achievable solution. In this study, the association with violence was present at the level of individual CD symptoms and indicates that it is useful to carefully assess these symptoms rather than just the presence of the full disorder. In summary, assessment of patients with schizophrenia should include careful consideration of pre-morbid CD symptoms, childhood adversities and substance misuse in adolescence, in order to inform a violence risk assessment.

9.9.2 Intervention

Early use of substances in patients with schizophrenia and pre-morbid CD is important in the risk of later violent behaviour. This emphasises the importance for clinicians of early intervention to treat substance abuse and CD with the target of reducing the risk of future violence. Effective treatments are available for CD, particularly parenting training (Weisz et al., 2004, Scott, 2008). In addition, there are also well-established treatment programmes for adolescent substance use disorders (Hogue et al., 2014). In adults with schizophrenia and a history of violence, it will be crucial to treat any co-morbid substance use disorders as part of the risk management plan.

The findings in this study relating to the association between childhood adversities and later violent behaviour are important for clinicians but also have wider societal implications. There is a need for the police and social services to respond effectively when children are being exposed to domestic violence in the home. All those who interact with children, including teachers and clinicians, have a responsibility to safeguard children from all forms of abuse. If it was possible to intervene earlier and in all cases of childhood abuse, then this would have an impact on reducing the risk of later violent behaviour in those with schizophrenia.

9.10 Future directions for research

Despite the global nature of violence, and a wealth of research, its quantification and causes still pose a significant research challenge. Broadly speaking, studies have attempted to quantify violence across several different dimensions; however, due to the complex and variable nature of violence, and methodological limitations, many of these measures remain largely unvalidated across populations. Data on violent acts are difficult to collect and are often done so retrospectively with a reliance on self-report measures. One of the main difficulties facing researchers is the need for large sample sizes in order to validate measures, while still preserving the richness of collected data. Despite this, future studies should move away from simply dichotomizing the presence or absence of violence to quantification using multiple sources and taking into consideration different dimensions of violence.

This study emphasises the importance of developmental pathways to violence among men with schizophrenia. Understanding the early influences on the complex trajectory towards violence in schizophrenia is crucial in order to reduce the risk of future violence. It is clear that CD increases the likelihood of cannabis use in early adolescence, which increases the risk of schizophrenia. Whilst there is an independent increase in the risk of violence associated with schizophrenia, pre-morbid CD and lifetime SUD are also associated with increases in the propensity to violence. Future prospective studies would benefit from focusing on the nature of these interactions and possible additive effects of these factors on the risk of violence in schizophrenia. In order to achieve this aim, large prospective longitudinal studies of individuals in early adolescence, with and without CD, are needed to explore if there is a common developmental pathway from childhood adversity, through CD, and drug use to schizophrenia, and finally violence.

Whilst a prospective study will be challenging and time consuming to undertake, there is learning from this study which can influence future retrospective studies of violence in schizophrenia. This research has contributed to the evidence base showing that pre-morbid CD is important in propensity to violence in schizophrenia, therefore future research should ensure that pre-morbid CD is assessed and considered in analyses. In addition, the importance of

childhood adversities has been demonstrated, including exposure to domestic violence. I would wish to explore this further in subsequent research, firstly to seek to replicate the finding in relation to domestic violence as it has not been demonstrated previously, and secondly to try to establish temporality in relation to onset and duration of different childhood adversities and the onset of symptoms of CD. If childhood adversities were the primary focus of a future study, then it would be possible to undertake more detailed assessments of this within a duration of assessments that is acceptable to participants. Overall, the key target for future research is that more detailed assessment of factors acting in childhood, including substance misuse, CD and adversities, is likely to be fruitful in increasing our understanding of violence in schizophrenia.

References

ABUSHUA'LEH, K. & ABU-AKEL, A. 2006. Association of psychopathic traits and symptomatology with violence in patients with schizophrenia. *Psychiatry Research,* 143**,** 205-211.

AFIFI, T. O., MCMILLAN, K. A., ASMUNDSON, G. J. G., PIETRZAK, R. H. & SAREEN, J. 2011. An examination of the relation between conduct disorder, childhood and adulthood traumatic events, and posttraumatic stress disorder in a nationally representative sample. *Journal of Psychiatric Research,* 45**,** 1564-1572.

ALEMANY, S., ARIAS B., FATJO-VILAS, M., VILLA, H., MOYA, J., IBANEZ, M. I., ORTET, G., GASTO, C. & FANANAS, L. 2014. Psychosis-inducing effects of cannabis are related to both childhood abuse and COMT genotypes. *Acta Psychiatrica Scandinavica*, 129, 54-62.

AMERICAN PSYCHIATRIC ASSOCIATION 2000. *Diagnostic and Statistical Manual of Mental Disorders,* Washington DC, American Psychiatric Association.

AMERICAN PSYCHIATRIC ASSOCIATION 2013. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5,* Washington DC, American Psychiatric Association.

ANDERSON, C. A. & BUSHMAN, B. J. 2002. Human aggression. *Annual Review of Psychology.*

ANDREASEN, N., CARPENTER, W., KANE, J., LASSER, R., MARDER, S. & WEINBERGER, D. 2005. Remission in schizophrenia: proposed criteria and rationale for consensus. *American Journal of Psychiatry,* 162**,** 441-449.

ANDREASEN, N. C., LIU, D., ZIEBELL, S., VORA, A. & HO, B. C. 2013. Relapse duration, treatment intensity, and brain tissue loss in schizophrenia: A prospective longitudinal MRI study. *American Journal of Psychiatry,* 170**,** 609-615.

APPELBAUM, P., ROBBINS, P. & MONAHAN, J. 2000. Violence and delusions: data from the MacArthur violence risk assessment study. *American Journal of Psychiatry,* 157**,** 566-572.

ARANGO, C., BARBA, A., GONZALEZ-SALVADOR, T. & ORDONEZ, A. 1999. Violence in inpatients with schizophrenia: a prospective study. *Schizophrenia Bulletin,* 25**,** 493-503.

ARSENEAULT, L., CANNON, M., POULTON, R., MURRAY, R., CASPI, A. & MOFFITT, T. E. 2002. Cannabis use in adolescence and risk for adult psychosis: Longitudinal prospective study. *British Medical Journal,* 325**,** 1212-1213.

ARSENEAULT, L., CANNON, M., WITTON, J. & MURRAY, R. 2004. Causal association between cannabis and psychosis: examination of the evidence. *British Journal of Psychiatry,* 184**,** 110-117.

ARSENEAULT, L., MOFFITT, T., CASPI, A., TAYLOR, P. & SILVA, P. 2000. Mental disorders and violence in a total birth cohort: results from the Dunedin study. *Archives of General Psychiatry,* 57**,** 979-986.

ASHBURNER, J. & FRISTON, K. J. 2000. Voxel-based morphometry - The methods. *NeuroImage,* 11**,** 805-821.

BARKATAKI, I., KUMARI, V., DAS, M., SUMICH, A., TAYLOR, P. & SHARMA, T. 2008. Neural correlates of deficient response inhibition in mentally disordered violent individuals. *Behavioral Sciences and the Law,* 26**,** 51-64.

BARKATAKI, I., KUMARI, V., DAS, M., TAYLOR, P. & SHARMA, T. 2006. Volumetric structural brain abnormalities in men with schizophrenia or antisocial personality disorder. *Behavioural Brain Research,* 169**,** 239-247.

BENNOUNA-GREENE, M., BENNOUNA-GREENE, V., BERNA, F. & DEFRANOUX, L. 2011. History of abuse and neglect in patients with schizophrenia who have a history of violence. *Child Abuse and Neglect,* 35**,** 329-332.

BERRY, K. & HADDOCK, G. 2008. The implementation of the NICE guidelines for schizophrenia: Barriers to the implementation of psychological interventions and recommendations for the future. *Psychology and Psychotherapy: Theory, Research and Practice,* 81**,** 419-436.

BHAKTA, S. G., ZHANG, J. P. & MALHOTRA, A. K. 2012. The COMT Met158 allele and violence in schizophrenia: A meta-analysis. *Schizophrenia Research*.

BHUI, K., ULLRICH, S., KALLIS, C. & COID, J. W. 2015. Criminal justice pathways to psychiatric care for psychosis. *British Journal of Psychiatry,* 207**,** 523-529.

BIFULCO, A., BERNAZZANI, O., MORAN, P. & JACOBS, C. 2005. The childhood experience of care and abuse questionnaire (CECA.Q): validation in a community series. *British Journal of Clinical Psychology,* 44**,** 563-581.

BIRCHWOOD, M., SMITH, J., DRURY, V., HEALY, J., MACMILLAN, F. & SLADE, M. 1994. A self-report insight scale for psychosis: Reliability, validity and sensitivity to change. *Acta Psychiatrica Scandinavica,* 89**,** 62-67.

BLAIR, R. J. R., LEIBENLUFT, E. & PINE, D. S. 2014. Conduct disorder and callous-unemotional traits in youth. *New England Journal of Medicine,* 371**,** 2207-2216.

BLEULER, E. 1911. *Dementia praecox oder die gruppe der schizophrenien,* Liepzig, Deuticke.

BO, S., ABU-AKEL, A., KONGERSLEV, M., HAAHR, U. H. & SIMONSEN, E. 2011. Risk factors for violence among patients with schizophrenia. *Clinical Psychology Review,* 31**,** 711-726.

BO, S., FORTH, A., KONGERSLEV, M., HAAHR, U. H., PEDERSEN, L. & SIMONSEN, E. 2013. Subtypes of aggression in patients with schizophrenia: The role of personality disorders. *Criminal Behaviour and Mental Health,* 23**,** 124-137.

BOCCARDI, M., BOCCHETTA, M., ARONEN, H. J., REPO-TIIHONEN, E., VAURIO, O., THOMPSON, P. M., TIIHONEN, J. & FRISONI, G. B. 2013. Atypical nucleus accumbens morphology in psychopathy: Another limbic piece in the puzzle. *International Journal of Law and Psychiatry,* 36**,** 157-167.

BOIS, C., WHALLEY, H. C., MCINTOSH, A. M. & LAWRIE, S. M. 2015. Structural magnetic resonance imaging markers of susceptibility and transition to schizophrenia: A review of familial and clinical high risk population studies. *Journal of Psychopharmacology,* 29**,** 144-154.

BORA, E., FORNITO, A., RADUA, J., WALTERFANG, M., SEAL, M., WOOD, S. J., YÜCEL, M., VELAKOULIS, D. & PANTELIS, C. 2011. Neuroanatomical abnormalities in schizophrenia: A multimodal voxelwise meta-analysis and meta-regression analysis. *Schizophrenia Research,* 127**,** 46-57.

BOSQUI, T. J., SHANNON, C., TIERNAN, B., BEATTIE, N., FERGUSON, J. & MULHOLLAND, C. 2014. Childhood trauma and the risk of violence in adulthood in a population with a psychotic illness. *Journal of Psychiatric Research*.

BOWERS, L., NIJMAN, H. & PALMSTIERNA, T. 2007. The attempted and actual assault scale (attacks). *International Journal of Methods in Psychiatric Research,* 16**,** 171-176.

BRUCE, M. & LAPORTE, D. 2015. Childhood trauma, antisocial personality typologies and recent violent acts among inpatient males with severe mental illness: Exploring an explanatory pathway. *Schizophrenia Research,* 162**,** 285-290.

BUCCI, S., BIRCHWOOD, M., TWIST, L., TARRIER, N., EMSLEY, R. & HADDOCK, G. 2013. Predicting compliance with command hallucinations: Anger, impulsivity and appraisals of voices' power and intent. *Schizophrenia Research,* 147**,** 163-168.

BUSS, A. & PERRY, M. 1992. The aggression questionnaire. *Journal of Personality and Social Psychology,* 63**,** 452-459.

CASEY, P. & KELLY, B. 2007. *Fish's Clinical Psychopathology: Signs and Symptoms in Psychiatry,* London, Gaskell.

CASPI, A., MOFFITT, T. E., CANNON, M., MCCLAY, J., MURRAY, R., HARRINGTON, H., TAYLOR, A., ARSENEAULT, L., WILLIAMS, B., BRAITHWAITE, A., POULTON, R. & CRAIG, I. W. 2005. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: Longitudinal evidence of a gene X environment interaction. *Biological Psychiatry,* 57**,** 1117-1127.

CERDA, M., DIGANGI, J., GALEA, S. & KOENEN, K. C. 2012. Epidemiologic research on interpersonal violence and common psychiatric disorders: Where do we go from here? . *Depression and Anxiety,* 29**,** 359-385.

CHAKOS, M. H., LIEBERMAN, J. A., BILDER, R. M., BORENSTEIN, M., LERNER, G., BOGERTS, B., WU, H., KINON, B. & ASHTARI, M. 1994. Increase in caudate nuclei volumes of first-episode schizophrenic patients taking antipsychotic drugs. *American Journal of Psychiatry,* 151**,** 1430-1436.

CHEN, Z., DENG, W., GONG, Q., HUANG, C., JIANG, L., LI, M., HE, Z., WANG, Q., MA, X., WANG, Y., CHUA, S. E., MCALONAN, G. M., SHAM, P. C., COLLIER, D. A., MCGUIRE, P. & LI, T. 2014. Extensive brain structural network abnormality in first-episode treatment-naive patients with schizophrenia: Morphometrical and covariation study. *Psychological Medicine,* 44**,** 2489-2501.

CHEUNG, P., SCHWEITZER, I., CROWLEY, K. & TUCKWELL, V. 1997a. Aggressive behaviour in schizophrenia: Role of state versus trait factors. *Psychiatry Research,* 72**,** 41-50.

CHEUNG, P., SCHWEITZER, I., CROWLEY, K. & TUCKWELL, V. 1997b. Violence in schizophrenia: Role of hallucinations and delusions. *Schizophrenia Research,* 26**,** 181-190.

COCCARO, E., BERMAN, M. E. & KAVOUSSI, R. 1997. Assessment of life history of aggression: development and psychometric characteristics. *Psychiatry Research,* 73**,** 147-157.

COID, J. & YANG, M. 2011. The impact of psychopathy on violence among the household population of Great Britain. *Social Psychiatry and Psychiatric Epidemiology,* 46**,** 473-480.

COID, J., YANG, M., ROBERTS, A., ULLRICH, S., MORAN, P., BEBBINGTON, P., BRUGHA, T., JENKINS, R., FARRELL, M., LEWIS, G. & SINGLETON, N. 2006. Violence and psychiatric morbidity in a national household population - A report from the British household survey. *American Journal of Epidemiology,* 164**,** 1199-1208.

COID, J. W., ULLRICH, S., BEBBINGTON, P., FAZEL, S. & KEERS, R. 2016. Paranoid Ideation and Violence: Meta-analysis of Individual Subject Data of 7 Population Surveys. *Schizophrenia Bulletin*.

COID, J. W., ULLRICH, S., KALLIS, C., KEERS, R., BARKER, D., COWDEN, F. & STAMPS, R. 2013. The relationship between delusions and violence: Findings from the East London first episode psychosis study. *JAMA Psychiatry,* 70**,** 465-471.

COLLIP, D., VAN WINKEL, R., PEERBOOMS, O., LATASTER, T., THEWISSEN, V., LARDINOIS, M., DRUKKER, M., RUTTEN, B. P., VAN OS, J. & MYIN-GERMEYS, I. 2011. COMT Val158Met-stress interaction in psychosis: Role of background psychosis risk. *CNS Neuroscience and Therapeutics,* 17**,** 612-619.

CONLEY, R. & KELLY, D. 2001. Management of treatment resistance in schizophrenia. *Society of Biological Psychiatry,* 50**,** 898-911.

CONRAD, K. J., RILEY, B. B., CONRAD, K. M., CHAN, Y. F. & DENNIS, M. L. 2010. Validation of the crime and violence scale (CVS) against the rasch measurement model including differences by gender, race, and age. *Evaluation Review,* 34**,** 83-115.

CRADDOCK, N. & OWEN, M. J. 2010. The Kraepelinian dichotomy - Going, going... but still not gone. *British Journal of Psychiatry,* 196**,** 92-95.

DAFFERN, M., HOWELLS, K., OGLOFF, J. & LEE, J. 2005. Individual characteristics predisposing patients to aggression in a forensic psychiatric hospital. *Journal of Forensic Psychiatry and Psychology,* 16**,** 729-746.

DARRELL-BERRY, H., BERRY, K. & BUCCI, S. 2016. The relationship between paranoia and aggression in psychosis: A systematic review. *Schizophrenia Research*.

DE OLIVEIRA-SOUZA, R., HARE, R. D., BRAMATI, I. E., GARRIDO, G. J., AZEVEDO IGNÁCIO, F., TOVAR-MOLL, F. & MOLL, J. 2008. Psychopathy as a disorder of the moral brain: Fronto-temporo-limbic grey matter reductions demonstrated by voxel-based morphometry. *NeuroImage,* 40**,** 1202-1213.

DEAN, K., WALSH, E., MORGAN, C., DEMJAHA, A., DAZZAN, P., MORGAN, K., LLOYD, T., FEARON, P., JONES, P. B. & MURRAY, R. M. 2007. Aggressive behaviour at first contact with services: Findings from the AESOP First Episode Psychosis Study. *Psychological Medicine,* 37**,** 547-557.

DI FORTI, M., MARCONI, A., CARRA, E., FRAIETTA, S., TROTTA, A., BONOMO, M., BIANCONI, F., GARDNER-SOOD, P., O'CONNOR, J., RUSSO, M., STILO, S. A., MARQUES, T. R., MONDELLI, V., DAZZAN, P., PARIANTE, C., DAVID, A. S., GAUGHRAN, F., ATAKAN, Z., IYEGBE, C., POWELL, J., MORGAN, C., LYNSKEY, M. & MURRAY, R. M. 2015. Proportion of patients in south London with first-episode psychosis attributable to use of high potency cannabis: A case-control study. *The Lancet Psychiatry,* 2**,** 233-238.

DOLAN, M. 2010. What imaging tells us about violence in anti-social men. *Criminal Behaviour and Mental Health,* 20**,** 199-214.

DOLAN, M. & FULLAM, R. 2009. Psychopathy and functional magnetic resonance imaging blood oxygenation level-dependent responses to emotional faces in violent patients with schizophrenia. *Biological Psychiatry,* 66**,** 570-577.

DOUGLAS, K. S., GUY, L. S. & HART, S. D. 2009. Psychosis as a Risk Factor for Violence to Others: A Meta-Analysis. *Psychological Bulletin,* 135**,** 679-706.

ELBOGEN, E. & JOHNSON, S. 2009. The intricate link between violence and mental disorder: results from the national epidemiologic survey on alcohol and related conditions. *Archives of General Psychiatry,* 66**,** 152-161.

ELLISON-WRIGHT, I. & BULLMORE, E. 2009. Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophrenia Research,* 108**,** 3-10.

ELLISON-WRIGHT, I. & BULLMORE, E. 2010. Anatomy of bipolar disorder and schizophrenia: A meta-analysis. *Schizophrenia Research,* 117**,** 1-12.

ELLISON-WRIGHT, I., GLAHN, D. C., LAIRD, A. R., THELEN, S. M. & BULLMORE, E. 2008. The anatomy of first-episode and chronic schizophrenia: An anatomical likelihood estimation meta-analysis. *American Journal of Psychiatry,* 165**,** 1015-1023.

ETTINGER, U., PICCHIONI, M., LANDAU, S., MATSUMOTO, K., VAN HAREN, N. E., MARSHALL, N., HALL, M. H., SCHULZE, K., TOULOPOULOU, T., DAVIES, N., RIBCHESTER, T., MCGUIRE, P. K. & MURRAY, R. M. 2007. Magnetic resonance imaging of the thalamus and adhesio interthalamica in twins with schizophrenia. *Archives of General Psychiatry,* 64**,** 401-409.

FANNING, J. R., BERMAN, M. E., MOHN, R. S. & MCCLOSKEY, M. S. 2011. Perceived threat mediates the relationship between psychosis proneness and aggressive behavior. *Psychiatry Research,* 186**,** 210-218.

FARRELL, M. S., WERGE, T., SKLAR, P., OWEN, M. J., OPHOFF, R. A., O'DONOVAN M, C., CORVIN, A., CICHON, S. & SULLIVAN, P. F. 2015. Evaluating historical candidate genes for schizophrenia. *Molecular Psychiatry,* 20**,** 555-562.

FAUL, F., ERDFELDER, E., LANG, A.-G. & BUCHNER, A. 2007. G*Power 3: A flexible statistical power analysis program for the social, behavioural, and biomedical sciences. *Behavior Research Methods,* 39**,** 175-191.

FAZEL, S., LANGSTROM, N., HJERN, A., GRANN, M. & LICHTENSTEIN, P. 2009. Schizophrenia, substance abuse and violent crime. *JAMA,* 301**,** 2016-2023.

FAZEL, S., WOLF, A., PALM, C. & LICHTENSTEIN, P. 2014. Violent crime, suicide, and premature mortality in patients with schizophrenia and related disorders: A 38-year total population study in Sweden. *The Lancet Psychiatry,* 1**,** 44-54.

FELTHOUS, A. R. 2008. Schizophrenia and impulsive aggression: A heuristic inquiry with forensic and clinical implications. *Behavioral Sciences and the Law,* 26**,** 735-758.

FIRST, M., GIBBON, M., SPITZER, R., WILLIAMS, J. & BENJAMIN, L. (eds.) 1997. *User's guide for the Structured Clinical Interview for DSM-IV Axis II Personality Disorders: SCID-II,* Washington: American Psychiatric Publishing.

FIRST, M., SPITZER, R., GIBBON, M. & WILLIAMS, J. (eds.) 2002. *Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition,* New York: New York State Psychiatric Institute.

FISHER, H. L., CRAIG, T. K., FEARON, P., MORGAN, K., DAZZAN, P., LAPPIN, J., HUTCHINSON, G., DOODY, G. A., JONES, P. B., MCGUFFIN, P., MURRAY, R. M., LEFF, J. & MORGAN, C. 2011. Reliability and comparability of psychosis patients' retrospective reports of childhood abuse. *Schizophrenia Bulletin,* 37**,** 546-553.

FITZSIMMONS, J., KUBICKI, M. & SHENTON, M. E. 2013. Review of functional and anatomical brain connectivity findings in schizophrenia. *Current Opinion in Psychiatry,* 26**,** 172-187.

FOLEY, D. L., EAVES, L. J., WORMLEY, B., SILBERG, J. L., MAES, H. H., KUHN, J. & RILEY, B. 2004. Childhood adversity, monoamine oxidase A genotype, and risk for conduct disorder. *Archives of General Psychiatry,* 61**,** 738-744.

FRESAN, A., CAMARENA, B., APIQUIAN, R., AGUILAR, A., URRACA, N. & NICOLINI, H. 2007. Association study of MAO-A and DRD4 genes in schizophrenic patients with aggressive behaviour. *Neuropsychobiology,* 55**,** 171-175.

FROGLEY, C., TAYLOR, D., DICKENS, G. & PICCHIONI, M. 2012. A systematic review of the evidence of clozapine's anti-aggressive effects. *International Journal of Neuropsychopharmacology,* 15**,** 1351-1371.

FULWILER, C., GROSSMAN, H., FORBES, C. & RUTHAZER, R. 1997. Early-onset substance abuse and community violence by outpatients with chronic mental illness. *Psychiatric Services,* 48**,** 1181-1185.

FULWILER, C. & RUTHAZER, R. 1999. Premorbid risk factors for violence in adult mental illness. *Comprehensive Psychiatry,* 40**,** 96-100.

FUSAR-POLI, P., SMIESKOVA, R., KEMPTON, M. J., HO, B. C., ANDREASEN, N. C. & BORGWARDT, S. 2013. Progressive brain changes in schizophrenia related to antipsychotic treatment? A meta-analysis of longitudinal MRI studies. *Neuroscience and Biobehavioral Reviews,* 37**,** 1680-1691.

GARDNER, D., MURPHY, A., O'DONNELL, H., CENTORRINO, F. & BALDESSARINI, R. 2010. International consensus study of antipsychotic dosing. *Amercan Journal of Psychiatry,* 167**,** 686-693.

GARETY, P. A., FOWLER, D. G., FREEMAN, D., BEBBINGTON, P., DUNN, G. & KUIPERS, E. 2008. Cognitive–behavioural therapy and family intervention for relapse prevention and symptom reduction in psychosis: randomised controlled trial. *The British Journal of Psychiatry,* 192**,** 412-423.

GIBBON, S., FERRITER, M. & DUGGAN, C. 2009. A comparison of the family and childhood backgrounds of hospitalised offenders with schizophrenia or personality disorder. *Criminal Behaviour and Mental Health,* 19**,** 207-218.

GLAHN, D. C., LAIRD, A. R., ELLISON-WRIGHT, I., THELEN, S. M., ROBINSON, J. L., LANCASTER, J. L., BULLMORE, E. & FOX, P. T. 2008. Meta-Analysis of Gray Matter Anomalies in Schizophrenia: Application of Anatomic Likelihood Estimation and Network Analysis. *Biological Psychiatry,* 64**,** 774-781.

GLENN, A. L., RAINE, A., YARALIAN, P. S. & YANG, Y. 2010. Increased Volume of the Striatum in Psychopathic Individuals. *Biological Psychiatry,* 67**,** 52-58.

GONZÁLEZ, R. A., KALLIS, C., ULLRICH, S., BARNICOT, K., KEERS, R. & COID, J. W. 2016. Childhood maltreatment and violence: Mediation through psychiatric morbidity. *Child Abuse and Neglect,* 52**,** 70-84.

GOPAL, Y. V. & VARIEND, H. 2005. First-episode schizophrenia: review of cognitive deficits and cognitive remediation. *Advances in Psychiatric Treatment,* 11**,** 38-44.

GREGORY, S., BLAIR, R. J., FFYTCHE, D., SIMMONS, A., KUMARI, V., HODGINS, S. & BLACKWOOD, N. 2015. Punishment and psychopathy: A case-control functional MRI investigation of reinforcement learning in violent antisocial personality disordered men. *The Lancet Psychiatry,* 2**,** 153-160.

GREGORY, S., FYYTCHE, D., SIMMONS, A., KUMARI, V., HOWARD, M., S., H. & BLACKWOOD, N. 2012. The antisocial brain: psychopathy matters. *Archives of General Psychiatry*.

GRELLA, C., HSER, Y., JOSHI, V. & ROUNDS-BRYANT, J. 2001. Drug treatment outcomes for adolescents with comorbid mental and substance use disorders. *Journal of Nervous and Mental Disease,* 189**,** 384-392.

GUAN, X., DONG, Z. Q., TIAN, Y. Y., WU, L. N., GU, Y., HU, Z. Q. & ZHANG, X. 2014. Lack of association between brain-derived neurotrophic factor Val66Met polymorphism and aggressive behavior in schizophrenia. *Psychiatry Research,* 215**,** 244-245.

GUNN, J. & ROBERTSON, G. 1976. Drawing a criminal profile. *British Journal of Criminology,* 16**,** 156-160.

GUPTA, C. N., CALHOUN, V. D., RACHAKONDA, S., CHEN, J., PATEL, V., LIU, J., SEGALL, J., FRANKE, B., ZWIERS, M. P., ARIAS-VASQUEZ, A., BUITELAAR, J., FISHER, S. E., FERNANDEZ, G., VAN ERP, T. G. M., POTKIN, S., FORD, J., MATHALON, D., MCEWEN, S., LEE, H. J., MUELLER, B. A., GREVE, D. N., ANDREASSEN, O., AGARTZ, I., GOLLUB, R. L., SPONHEIM, S. R., EHRLICH, S., WANG, L., PEARLSON, G., GLAHN, D. C., SPROOTEN, E., MAYER, A. R., STEPHEN, J., JUNG, R. E., CANIVE, J., BUSTILLO, J. & TURNER, J. A. 2015. Patterns of gray matter abnormalities in schizophrenia based on an international mega-analysis. *Schizophrenia Bulletin,* 41**,** 1133-1142.

GUY, L. S. & DOUGLAS, K. S. 2006. Examining the utility of the PCL:SV as a screening measure using competing factor models of psychopathy. *Psychological Assessment,* 18**,** 225-230.

HADDOCK, G., EISNER, E., DAVIES, G., COUPE, N. & BARROWCLOUGH, C. 2013. Psychotic symptoms, self-harm and violence in individuals with schizophrenia and substance misuse problems. *Schizophrenia Research*.

HAIJMA, S. V., VAN HAREN, N., CAHN, W., KOOLSCHIJN, P. C. M. P., HULSHOFF POL, H. E. & KAHN, R. S. 2013. Brain volumes in schizophrenia: A meta-analysis in over 18 000 subjects. *Schizophrenia Bulletin,* 39**,** 1129-1138.

HAMSHERE, M. L., WALTERS, J. T. R., SMITH, R., RICHARDS, A. L., GREEN, E., GROZEVA, D., JONES, I., FORTY, L., JONES, L., GORDON-SMITH, K., RILEY, B., O'NEILL, T., KENDLER, K. S., SKLAR, P., PURCELL, S., KRANZ, J., MORRIS, D., GILL, M., HOLMANS, P., CRADDOCK, N., CORVIN, A., OWEN, M. J. & O'DONOVAN, M. C. 2014. Genome-wide significant associations in schizophrenia to ITIH3/4, CACNA1C and SDCCAG8, and extensive replication of associations reported by the Schizophrenia PGC. *Nature,* 508**,** 708-712.

HAN, D., PARK, D., NA, C., KEE, B. & LEE, Y. 2004. Association of aggressive behaviour in Korean male schizophrenic patients with polymorphisms in the serotonin transporter promoter and catecholamine-O-methyltransferase genes. *Psychiatry Research,* 129**,** 29-37.

HAN, D. H., BAIK, S. K., KYUNG, J. M., YOUNG, S. L., NA, C., DOO, B. P. & IN, K. L. 2006. Effects of catechol-O-methyltransferase Val158Met polymorphism on the

cognitive stability and aggression in the first-onset schizophrenic patients. *NeuroReport,* 17**,** 95-99.
HANSSEN, M., BAK, M., BIJL, R., VOLLEBERGH, W. & VAN OS, J. 2005. The incidence and outcome of subclinical psychotic experiences in the general population. *British Journal of Clinical Psychology,* 44**,** 181-191.
HARE, R. D., HARPUR, T. J., HAKSTIAN, A. R., FORTH, A. E., HART, S. D. & NEWMAN, J. P. 1990. The Revised Psychopathy Checklist: Reliability and Factor Structure. *Psychological Assessment,* 2**,** 338-341.
HARRIS, A. W. F., LARGE, M. M., REDOBLADO-HODGE, A., NIELSSEN, O., ANDERSON, J. & BRENNAN, J. 2010. Clinical and cognitive associations with aggression in the first episode of psychosis. *Australian and New Zealand Journal of Psychiatry,* 44**,** 85-93.
HARRIS, S. 2014. *Identifying neurocognitive factors associated with violence in schizophrenia.* PhD, King's College London.
HARRIS, S., OAKLEY, C. & PICCHIONI, M. 2013. Quantifying violence in mental health research. *Aggression and Violent Behavior,* 18**,** 695-701.
HART, S., COX, D. & HARE, R. 1995. *The Hare Psychopathy Checklist: Screening Version (PCL:SV),* Toronto, Multi-Health Systems.
HEADS, T., TAYLOR, P. & LEESE, M. 1997. Childhood experiences of patients with schizophrenia and a history of violence: a special hospital sample. *Criminal Behaviour and Mental Health,* 7**,** 117-130.
HENQUET, C., MURRAY, R., LINSZEN, D. & VAN OS, J. 2005. The environment and schizophrenia: The role of cannabis use. *Schizophrenia Bulletin,* 31**,** 608-612.
HENQUET, C., ROSA, A., DELESPAUL, P., PAPIOL, S., FAŇANÁS, L., VAN OS, J. & MYIN-GERMEYS, I. 2009. COMT Val158Met moderation of cannabis-induced psychosis: A momentary assessment study of 'switching on' hallucinations in the flow of daily life. *Acta Psychiatrica Scandinavica,* 119**,** 156-160.
HEPGUL, N., PARIANTE, C. M., DIPASQUALE, S., DIFORTI, M., TAYLOR, H., MARQUES, T. R., MORGAN, C., DAZZAN, P., MURRAY, R. M. & MONDELLI, V. 2012. Childhood maltreatment is associated with increased body mass index and increased C-reactive protein levels in first-episode psychosis patients. *Psychological Medicine,* 42**,** 1893-1901.
HOCHBERG, Y. & BENJAMINI, Y. 1990. More powerful procedures for multiple significance testing. *Statistics in Medicine,* 9**,** 811-818.
HODGINS, S. 2008. Violent behaviour among people with schizophrenia: a framework for investigations of causes, and effective treatment, and prevention. *Philosophical Transactions of the Royal Society of Biological Sciences,* 363**,** 2505-2518.
HODGINS, S., CREE, A., ALDERTON, J. & MAK, T. 2008. From conduct disorder to severe mental illness: associations with aggressive behaviour, crime and victimization. *Psychological Medicine,* 38**,** 975-987.
HODGINS, S., HISCOKE, U. & FREESE, R. 2003. The antecedents of aggressive behavior among men with schizophrenia: a prospective investigation of patients in community treatment. *Behavioural Sciences and the Law,* 21**,** 523-546.
HODGINS, S., PIATOSA, M. J. & SCHIFFER, B. 2014. Violence among people with schizophrenia: phenotypes and neurobiology. *Current topics in behavioral neurosciences,* 17**,** 329-368.
HODGINS, S., TIIHIONEN, J. & ROSS, D. 2005. The consequences of conduct disorder for males who develop schizophrenia: associations with criminality, aggressive behaviour, substance use and psychiatric services. *Schizophrenia Research,* 78**,** 323-335.
HOGUE, A., HENDERSON, C., OZECHOWSKI, T. & ROBBINS, M. 2014. Evidence base on outpatient behavioral treatments for adolescent substance use: updates and recommendations 2007-2013. *Journal of Clinical Child and Adolescent Psychology,* 43**,** 695-720.

HONG, J. P., LEE, J. S., CHUNG, S., JUNG, J., YOO, H. K., CHANG, S. M. & KIM, C. Y. 2008. New functional single nucleotide polymorphism (Ala72Ser) in the COMT gene is associated with aggressive behavior in male schizophrenia. *American journal of medical genetics. Part B, Neuropsychiatric genetics : the official publication of the International Society of Psychiatric Genetics,* 147 B**,** 658-660.

HOPFER, C., SALOMONSEN-SAUTEL, S., MIKULICH-GILBERTSON, S., MIN, S. J., MCQUEEN, M., CROWLEY, T., YOUNG, S., CORLEY, R., SAKAI, J., THURSTONE, C., HOFFENBERG, A., HARTMAN, C. & HEWITT, J. 2013. Conduct disorder and initiation of substance use: A prospective longitudinal study. *Journal of the American Academy of Child and Adolescent Psychiatry,* 52**,** 511-518.e4.

HOPTMAN, M., D'ANGELO, D., CATALANO, D., MAURO, C., SHEHZAD, Z., KELLY, A., CASTELLANOS, F., JAVITT, D. & MILHAM, M. 2010. Amygdalofrontal functional disconnectivity and aggression in schizophrenia. *Schizophrenia Bulletin,* 36**,** 1020-1028.

HOPTMAN, M., VOLAVKA, J., JOHNSON, G., WEISS, E., BILDER, R. & LIM, K. 2002. Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study. *Biological Psychiatry,* 52**,** 9-14.

HOPTMAN, M., VOLAVKA, J., WEISS, E., CZOBOR, P., SZESZKO, P., GERIG, G., CHAKOS, M., BLOCHER, J., CITROME, L., LINDENMAYER, J., SHEITMAN, B., LIEBERMAN, J. & BILDER, R. 2005. Quantitative MRI measures of orbitofrontal cortex in patients with chronic schizophrenia or schizoaffective disorder. *Psychiatry Research: Neuroimaging,* 140**,** 133-145.

HOPTMAN, M. J. & ANTONIUS, D. 2011. Neuroimaging correlates of aggression in schizophrenia: An update. *Current Opinion in Psychiatry,* 24**,** 100-106.

HOPTMAN, M. J., ANTONIUS, D., MAURO, C. J., PARKER, E. M. & JAVITT, D. C. 2014. Cortical thinning, functional connectivity, and mood-related impulsivity in schizophrenia: relationship to aggressive attitudes and behavior. *The American journal of psychiatry,* 171**,** 939-948.

HOPTMAN, M. J., VOLAVKA, J., CZOBOR, P., GERIG, G., CHAKOS, M., BLOCHER, J., CITROME, L. L., SHEITMAN, B., LINDENMAYER, J. P., LIEBERMAN, J. A. & BILDER, R. M. 2006. Aggression and quantitative MRI measures of caudate in patients with chronic schizophrenia or schizoaffective disorder. *Journal of Neuropsychiatry and Clinical Neurosciences,* 18**,** 509-515.

HOPTMAN, M. J., YATES, K. F., PATALINJUG, M. B., WACK, R. C. & CONVIT, A. 1999. Clinical prediction of assaultive behavior among male psychiatric patients at a maximum-security forensic facility. *Psychiatric Services,* 50**,** 1461-1466.

JAUHAR, S., MCKENNA, P. J., RADUA, J., FUNG, E., SALVADOR, R. & LAWS, K. R. 2014. Cognitive-behavioural therapy for the symptoms of schizophrenia: systematic review and meta-analysis with examination of potential bias. *The British Journal of Psychiatry,* 204**,** 20-29.

JONES, G., ZAMMIT, S., NORTON, N., HAMSHERE, M., JONES, S., MILHAM, C., SANDERS, R., MCCARTHY, G., JONES, L., CARDNO, A., GRAY, M., MURPHY, K. & OWEN, M. 2001. Aggressive behaviour in patients with schizophrenia is associated with catechol-O-methyltransferase genotype. *British Journal of Psychiatry,* 179**,** 351-355.

JOYAL, C., PUTKONEN, A., MANCINI-MARÏE, A., HODGINS, S., KONONEN, M., BOULAY, L., PIHLAJAMAKI, M., SOININEN, H., STIP, E., TIIHONEN, J. & ARONEN, H. 2007. Violent persons with schizophrenia and comorbid disorders: a functional magnetic resonance imaging study. *Schizophrenia Research,* 91**,** 97-102.

KAHN, R. S., FLEISCHHACKER, W. W., BOTER, H., DAVIDSON, M., VERGOUWE, Y., KEET, I. P. M., GHEORGHE, M. D., RYBAKOWSKI, J. K., GALDERISI, S., LIBIGER, J., HUMMER, M., DOLLFUS, S., LOPEZ-IBOR, J. J., HRANOV, L. G., GAEBEL, W., PEUSKENS, J., LINDEFORS, N., RIECHER-ROSSLER, A. &

GROBBEE, D. E. 2008. Effectiveness of antipsychotic drugs in first-episode schizophrenia andd schizophreniform disorder: an open randmomised clinical trial. *Lancet,* 371**,** 1085-1097.

KAHN, R. S., LINSZEN, D. H., VAN OS, J., WIERSMA, D., BRUGGEMAN, R., CAHN, W., DE HAAN, L., KRABBENDAM, L. & MYIN-GERMEYS, I. 2011. Evidence that familial liability for psychosis is expressed as differential sensitivity to cannabis: An analysis of patient-sibling and sibling-control pairs. *Archives of General Psychiatry,* 68**,** 138-147.

KAVANAGH, D. H., TANSEY, K. E., O'DONOVAN, M. C. & OWEN, M. J. 2015. Schizophrenia genetics: Emerging themes for a complex disorder. *Molecular Psychiatry,* 20**,** 72-76.

KAY, S., FISZBEIN, A. & OPLER, L. 1987. The positive and negative syndrome scale for schizophrenia (PANSS). *Schizophrenia Bulletin,* 13**,** 261-276.

KAY, S., WOLKENFELD, F. & MURRILL, L. 1988. Profiles of aggression among psychiatric patients. Nature and prevalence. *J Nerv Ment Dis,* 176**,** 539-546.

KEERS, R., ULLRICH, S., DESTAVOLA, B. L. & COID, J. W. 2014. Association of violence with emergence of persecutory delusions in untreated schizophrenia. *American Journal of Psychiatry,* 171**,** 332-339.

KELLEHER, I., KEELEY, H., CORCORAN, P., RAMSAY, H., WASSERMAN, C., CARLI, V., SARCHIAPONE, M., HOVEN, C. & WASSERMAN, D. 2013. Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. *American Journal of Psychiatry,* 170**,** 734-741.

KESSLER, R. C., DAVIS, C. G. & KENDLER, K. S. 1997. Childhood adversity and adult psychiatric disorder in the US National Comorbidity Survey. *Psychological Medicine,* 27**,** 1101-1119.

KHALIFEH, H., MORAN, P., BORSCHMANN, R., DEAN, K., HART, C., HOGG, J., OSBORN, D., JOHNSON, S. & HOWARD, L. M. 2015. Domestic and sexual violence against patients with severe mental illness. *Psychological Medicine,* 45**,** 875-886.

KIM-COHEN, J., CASPI, A., MOFFITT, T. E., HARRINGTON, H., MILNE, B. J. & POULTON, R. 2003. Prior juvenile diagnoses in adults with mental disorder: Developmental follow-back of a prospective-longitudinal cohort. *Archives of General Psychiatry,* 60**,** 709-717.

KIM, Y. R., KIM, J. H., KIM, S. J., LEE, D. & MIN, S. K. 2008. Catechol-O-methyltransferase Val158Met polymorphism in relation to aggressive schizophrenia in a Korean population. *European Neuropsychopharmacology,* 18**,** 820-825.

KIROV, G., REES, E. & WALTERS, J. 2015. What a psychiatrist needs to know about copy number variants. *Advances in Psychiatric Treatment,* 21**,** 157-163.

KOEN, L., KINNEAR, C., CORFIELD, V., EMSLEY, R., JORDAAN, E., KEYTER, N., MOOLMAN-SMOOK, J., STEIN, D. & NIEHAUS, D. 2004. Violence in male patients with schizophrenia: risk markers in a South African population. *Australian and New Zealand Journal of Psychiatry,* 38**,** 254-259.

KOH, K. B., CHOI, E. H., LEE, Y. J., HAN, M., CHOI, S. S., KIM, S. W. & LEE, M. G. 2012. The relation of serotonin-related gene and COMT gene polymorphisms with criminal behavior in schizophrenic disorder. *Journal of Clinical Psychiatry,* 73**,** 159-163.

KOTLER, M., BARAK, P., COHEN, H., AVERBUCH, I., GRINSHPOON, A., GRITSENKO, I., NEMANOV, L. & EBSTEIN, R. 1999. Homicidal behavior in schizophrenia associated with a genetic polymorphism determining low catechol O-methyltransferase (COMT) activity. *American Journal of Medical Genetics (Neuropsychiatric Genetics),* 88**,** 628–633.

KRAKOWSKI, M., CZOBOR, P. & CHOU, J. 1999. Course of violence in patients with schizophrenia: relationship to clinical symptoms. *Schizophrenia Bulletin,* 25**,** 505-517.

KRAKOWSKI, M. I. & CZOBOR, P. 2012. The denial of aggression in violent patients with schizophrenia. *Schizophrenia Research,* 141**,** 228-233.

KUMARI, V., AASEN, I., TAYLOR, P., H. FFYTCHE, D., DAS, M., BARKATAKI, I., GOSWAMI, S., O'CONNELL, P., HOWLETT, M., WILLIAMS, S. & SHARMA, T. 2006. Neural dysfunction and violence in schizophrenia: an fMRI investigation. *Schizophrenia Research,* 84**,** 144-164.

KUMARI, V., BARKATAKI, I., GOSWAMIA, S., FLORAA, S., DAS, M. & TAYLOR, P. 2009a. Dysfunctional, but not functional, impulsivity is associated with a history of seriously violent behaviour and reduced orbitofrontal and hippocampal volumes in schizophrenia. *Psychiatry Research: Neuroimaging,* 173**,** 39-44.

KUMARI, V., DAS, M., HODGINS, S., ZACHARIAH, E., BARKATAKI, I., HOWLETT, M. & SHARMA, T. 2005. Association between violent behaviour and impaired prepulse inhibition of the startle response in antisocial personality disorder and schizophrenia. *Behavioural Brain Research,* 158**,** 159-166.

KUMARI, V., DAS, M., TAYLOR, P., BARKATAKI, I., ANDREW, C., SUMICH, A., WILLIAMS, S. C. R. & FFYTCHE, D. H. 2009b. Neural and behavioural responses to threat in men with a history of serious violence and schizophrenia or antisocial personality disorder. *Schizophrenia Research,* 110**,** 47-58.

KUMARI, V., GUDJONSSON, G. H., RAGHUVANSHI, S., BARKATAKI, I., TAYLOR, P., SUMICH, A., DAS, K., KUIPERS, E., FFYTCHE, D. H. & DAS, M. 2013. Reduced thalamic volume in men with antisocial personality disorder or schizophrenia and a history of serious violence and childhood abuse. *European Psychiatry,* 28**,** 225-234.

LAAJASALO, T., SALENIUS, S., LINDBERG, N., REPO-TIIHONEN, E. & HÄKKÄNEN-NYHOLM, H. 2011. Psychopathic traits in Finnish homicide offenders with schizophrenia. *International Journal of Law and Psychiatry,* 34**,** 324-330.

LACADIE, C. M., FULBRIGHT, R. K., RAJEEVAN, N., CONSTABLE, R. T. & PAPADEMETRIS, X. 2008. More accurate Talairach coordinates for neuroimaging using non-linear registration. *NeuroImage,* 42**,** 717-725.

LACHMAN, H., NOLAN, K., MOHR, P., SAITO, T. & VOLAVKA, J. 1998. Association between catechol O-methyltransferase genotype and violence in schizophrenia and schizoaffective disorder. *American Jounal of Psychiatry,* 155**,** 835-837.

LAMSMA, J. & HARTE, J. M. 2015. Violence in psychosis: Conceptualizing its causal relationship with risk factors. *Aggression and Violent Behavior,* 24**,** 75-82.

LANCASTER, J., WOLDORFF, M., PARSONS, L., LIOTTI, M., FREITAS, C., RAINEY, L., KOCHUNOV, P., NICKERSON, D., MIKITEN, S. & FOX, P. 2000. Automated Talairach Atlas labels for functional brain mapping. *Human Brain Mapping,* 10**,** 120-131.

LANGEVELD, J., BJØRKLY, S., AUESTAD, B., BARDER, H., EVENSEN, J., TEN VELDEN HEGELSTAD, W., JOA, I., JOHANNESSEN, J. O., LARSEN, T. K., MELLE, I., OPJORDSMOEN, S., RØSSBERG, J. I., RUND, B. R., SIMONSEN, E., VAGLUM, P., MCGLASHAN, T. & FRIIS, S. 2014. Treatment and violent behavior in persons with first episode psychosis during a 10-year prospective follow-up study. *Schizophrenia Research,* 156**,** 272-276.

LANGLEY, K., HERON, J., O'DONOVAN, M. C., OWEN, M. J., THAPAR, A. 2010. Genotype link with extreme antisocial behaviour: The contribution of cognitive pathways. *Archives of General Psychiatry*, 67, 1317-1323.

LARGE, M. M. & NIELSSEN, O. 2011. Violence in first-episode psychosis: A systematic review and meta-analysis. *Schizophrenia Research,* 125**,** 209-220.

LEASK, S. J. 2004. Environmental influences in schizophrenia: the known and the unknown. *Advances in Psychiatric Treatment,* 10**,** 323-330.

LEUCHT, S., TARDY, M., KOMOSSA, K., HERES, S., KISSLING, W., SALANTI, G. & DAVIS, J. M. 2012. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: A systematic review and meta-analysis. *The Lancet,* 379**,** 2063-2071.

LICHTENSTEIN, P., YIP, B. H., BJÖRK, C., PAWITAN, Y., CANNON, T. D., SULLIVAN, P. F. & HULTMAN, C. M. 2009. Common genetic determinants of schizophrenia and bipolar disorder in Swedish families: a population-based study. *The Lancet,* 373**,** 234-239.

LINK, B. & STUEVE, A. 1994. Psychotic symptoms and the violent/illegal behaviour of mental patients compared to the community. *In:* MONAHAN, J. & STEADMAN, H. (eds.) *Violence and Mental Disorder: Development in Risk Assessment.* Chicago: University of Chicago Press.

LINK, B. G., STUEVE, A. & PHELAN, J. 1998. Psychotic symptoms and violent behaviors: Probing the components of 'threat/control-override' symptoms. *Social Psychiatry and Psychiatric Epidemiology,* 33**,** S55-S60.

LUI, S., DENG, W., HUANG, X., JIANG, L., MA, X., CHEN, H., ZHANG, T., LI, X., LI, D., ZOU, L., TANG, H., ZHOU, X. J., MECHELLI, A., COLLIER, D. A., SWEENEY, J. A., LI, T. & GONG, Q. 2009. Association of cerebral deficits with clinical symptoms in antipsychotic-naive first-episode schizophrenia: An optimized voxel-based morphometry and resting state functional connectivity study. *American Journal of Psychiatry,* 166**,** 196-205.

MALCOLM, C. P., PICCHIONI, M. M., DIFORTI, M., SUGRANYES, G., COOKE, E., JOSEPH, C., MCQUEEN, G., PAPARELLI, A., STILO, S., O'CONNOR, J., MORGAN, C., MURRAY, R. M. & HODGINS, S. 2011. Pre-morbid Conduct Disorder symptoms are associated with cannabis use among individuals with a first episode of psychosis. *Schizophrenia Research,* 126**,** 81-86.

MANIGLIO, R. 2015. Significance, Nature, and Direction of the Association Between Child Sexual Abuse and Conduct Disorder: A Systematic Review. *Trauma, Violence, and Abuse,* 16**,** 241-257.

MAXWELL, M. 1992. Family Interview for Genetic Studies (FIGS). Rockville: National Institute of Mental Health.

MCGREGOR, K., CASTLE, D. & DOLAN, M. 2012. Schizophrenia spectrum disorders, substance misuse and the four-facet model of psychopathy: the relationship to violence. *Schizophrenia Bulletin,* 136**,** 116-121.

MCNIEL, D. E., EISNER, J. P. & BINDER, R. L. 2000. The relationship between command hallucinations and violence. *Psychiatric Services,* 51**,** 1288-1292.

MEEHAN, J., FLYNN, S., HUNT, I., ROBINSON, J., BICKLEY, H., PARSONS, R., AMOS, T., KAPUR, N., APPLEBY, L. & SHAW, J. 2006. Perpetrators of homicide with schizophrenia: a national clinical survey in England and Wales. *Psychiatric Services,* 57**,** 1648-1651.

MICHIE, C. & COOKE, D. 2006. The structure of violent behavior: a hierarchical model. *Criminal Justice and Behavior,* 33**,** 706-737.

MODINOS, G., IYEGBE, C., PRATA, D., RIVERA, M., KEMPTON, M. J., VALMAGGIA, L. R., SHAM, P. C., VAN OS, J. & MCGUIRE, P. 2013. Molecular genetic gene-environment studies using candidate genes in schizophrenia: A systematic review. *Schizophrenia Research,* 150**,** 356-365.

MORGAN, C., CHARALAMBIDES, M., HUTCHINSON, G. & MURRAY, R. M. 2010. Migration, ethnicity, and psychosis: Toward a sociodevelopmental model. *Schizophrenia Bulletin,* 36**,** 655-664.

MORGAN, C., KIRKBRIDGE, J., LEFF, J., CRAIG, T., HUTCHINSON, G., MCKENZIE, K., MORGAN, K., DAZZAN, P., DOODY, G. A., JONES, P., MURRAY, R. & FEARON, P. 2007. Parental separation, loss and psychosis in different ethnic groups: a case-control study. *Psychological Medicine,* 37**,** 495-503.

MORGAN, C., REININGHAUS, U., REICHENBERG, A., FRISSA, S., HOTOPF, M. & HATCH, S. L. 2014. Adversity, cannabis use and psychotic experiences: Evidence of cumulative and synergistic effects. *British Journal of Psychiatry,* 204**,** 346-353.

MORIN, L. & FRANCK, N. 2017. Rehabilitation interventions to promote recovery from schizophrenia: A systematic review. *Frontiers in Psychiatry,* 8.

MORRISON, E. 1993. The measurement of aggrsssion and violence in hospitalized psychiatric patients. *International Journal of Nursing Studies,* 30**,** 51-64.

MOUCHLIANITIS, E., MCCUTCHEON, R. & HOWES, O. D. 2016. Brain-imaging studies of treatment-resistant schizophrenia: A systematic review. *The Lancet Psychiatry,* 3**,** 451-463.

MUESER, K. T., CROCKER, A. G., FRISMAN, L. B., DRAKE, R. E., COVELL, N. H. & ESSOCK, S. M. 2006. Conduct disorder and antisocial personality disorder in persons with severe psychiatric and substance use disorders. *Schizophrenia Bulletin,* 32**,** 626-636.

MUESER, K. T., DRAKE, R. E., ACKERSON, T. H., ALTERMAN, A. I., MILES, K. M. & NOORDSY, D. L. 1997. Antisocial personality disorder, conduct disorder, and substance abuse in schizophrenia. *Journal of Abnormal Psychology,* 106**,** 473-477.

MÜLLER, J. L., GÄNßBAUER, S., SOMMER, M., DÖHNEL, K., WEBER, T., SCHMIDT-WILCKE, T. & HAJAK, G. 2008. Gray matter changes in right superior temporal gyrus in criminal psychopaths. Evidence from voxel-based morphometry. *Psychiatry Research - Neuroimaging,* 163**,** 213-222.

MURPHY, K. C., JONES, L. A. & OWEN, M. J. 1999. High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry,* 56**,** 940-945.

MURRAY, R. M. & LEWIS, S. W. 1988. Is schizophrenia a neurodevelopmental disorder? *British medical journal (Clinical research ed.),* 296**,** 63.

NARAYAN, V. M., NARR, K. L., KUMARI, V., WOODS, R. P., THOMPSON, P. M., TOGA, A. W. & SHARMA, T. 2007. Regional cortical thinning in subjects with violent antisocial personality disorder or schizophrenia. *American Journal of Psychiatry,* 164**,** 1418-1427.

NATHAN, R., ROLLINSON, L., HARVEY, K. & HILL, J. 2003. The Liverpool Violence Assessment: an investigator-based measure of violence. *Criminal Behaviour and Mental Health,* 13**,** 106-120.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE 2015. Psychosis and schizophrenia in adults: quality standard. National Institute for Health and Care Excellence.

NEDERLOF, A. F., MURIS, P. & HOVENS, J. E. 2011. Threat/control-override symptoms and emotional reactions to positive symptoms as correlates of aggressive behavior in psychotic patients. *Journal of Nervous and Mental Disease,* 199**,** 342-347.

NENADIC, I., DIETZEK, M., SCHÖNFELD, N., LORENZ, C., GUSSEW, A., REICHENBACH, J. R., SAUER, H., GASER, C. & SMESNY, S. 2015. Brain structure in people at ultra-high risk of psychosis, patients with first-episode schizophrenia, and healthy controls: A VBM study. *Schizophrenia Research,* 161**,** 169-176.

NIKOLAC PERKOVIC, M., SVOB STRAC, D., NEDIC ERJAVEC, G., UZUN, S., PODOBNIK, J., KOZUMPLIK, O., VLATKOVIC, S. & PIVAC, N. 2016. Monoamine oxidase and agitation in psychiatric patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*.

NOLAN, K., VOLAVKA, J., LACHMAN, H. & SAITO, T. 2000. An association between a polymorphism of the tryptophan hydroxylase gene and aggression in schizophrenia and schizoaffective disorder. *Psychiatric Genetics,* 10**,** 109-115.

NOLAN, K. A., BILDER, R. M., LACHMAN, H. M. & VOLAVKA, J. 2004. Catechol O-Methyltransferase Val158Met Polymorphism in Schizophrenia: Differential Effects of Val and Met Alleles on Cognitive Stability and Flexibility. *American Journal of Psychiatry,* 161**,** 359-361.

OAKLEY, C., HARRIS, S., FAHY, T., MURPHY, D. & PICCHIONI, M. 2016. Childhood adversity and conduct disorder: A developmental pathway to violence in schizophrenia. *Schizophrenia Research*.

OHI, K., MATSUDA, Y., SHIMADA, T., YASUYAMA, T., OSHIMA, K., SAWAI, K., KIHARA, H., NITTA, Y., OKUBO, H., UEHARA, T. & KAWASAKI, Y. 2016. Structural alterations of the superior temporal gyrus in schizophrenia: Detailed subregional differences. *European Psychiatry,* 35**,** 25-31.

OKUGAWA, G., NOBUHARA, K., TAKASE, K., SAITO, Y., YOSHIMURA, M. & KINOSHITA, T. 2007. Olanzapine increases grey and white matter volumes in the caudate nucleus of patients with schizophrenia. *Neuropsychobiology,* 55**,** 43-46.

OYEBODE, F. 2008. *Sims' Symptoms in the Mind: An Introduction to Descriptive Psychopathology,* London, Saunders Elsevier.

PERERA, U. & TAYLOR, M. 2014. NICE CG178 on psychosis - an evidence-based guideline? *The Journal of Prescribing and Medicines Management,* 2**5,** 6-8.

PFAMMATTER, M., JUNGHAN, U. M. & BRENNER, H. D. 2006. Efficacy of Psychological Therapy in Schizophrenia: Conclusions From Meta-analyses. *Schizophrenia Bulletin,* 32**,** S64-S80.

PICCHIONI, M. M. & MURRAY, R. M. 2007. Clinical Review: Schizophrenia. *British Medical Journal* 335**,** 91-5.

PURCELL, S. M., WRAY, N. R., STONE, J. L., VISSCHER, P. M., O'DONOVAN, M. C., SULLIVAN, P. F., RUDERFER, D. M., MCQUILLIN, A., MORRIS, D. W., OĜDUSHLAINE, C. T., CORVIN, A., HOLMANS, P. A., OĜDONOVAN, M. C., MACGREGOR, S., GURLING, H., BLACKWOOD, D. H. R., CRADDOCK, N. J., GILL, M., HULTMAN, C. M., KIROV, G. K., LICHTENSTEIN, P., MUIR, W. J., OWEN, M. J., PATO, C. N., SCOLNICK, E. M., ST CLAIR, D., WILLIAMS, N. M., GEORGIEVA, L., NIKOLOV, I., NORTON, N., WILLIAMS, H., TONCHEVA, D., MILANOVA, V., THELANDER, E. F., O'DUSHLAINE, C. T., KENNY, E., QUINN, E. M., CHOUDHURY, K., DATTA, S., PIMM, J., THIRUMALAI, S., PURI, V., KRASUCKI, R., LAWRENCE, J., QUESTED, D., BASS, N., CROMBIE, C., FRASER, G., LEH KUAN, S., WALKER, N., MCGHEE, K. A., PICKARD, B., MALLOY, P., MACLEAN, A. W., VAN BECK, M., PATO, M. T., MEDEIROS, H., MIDDLETON, F., CARVALHO, C., MORLEY, C., FANOUS, A., CONTI, D., KNOWLES, J. A., PAZ FERREIRA, C., MACEDO, A., HELENA AZEVEDO, M., KIRBY, A. N., FERREIRA, M. A. R., DALY, M. J., CHAMBERT, K., KURUVILLA, F., GABRIEL, S. B., ARDLIE, K., MORAN, J. L. & SKLAR, P. 2009. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature,* 460**,** 748-752.

PURI, B., COUNSELL, S., SAEED, N., BUSTOS, M., TREASADEN, I. & BYDDER, G. 2008. Regional grey matter volumetric changes in forensic schizophrenia patients: an MRI study comparing the brain structure of patients who have seriously and violently offended with that of patients who have not. *BMC Psychiatry,* 8**,** 56.

RAINE, A. 2018. Antisocial personality disorder as a neurodevelopmental disorder. *Annual Review of Clinical Psychology*, 14, 259-289.

RAINE, A. & YANG, Y. 2006. Neural foundations to moral reasoning and antisocial behavior. *Social cognitive and affective neuroscience,* 1**,** 203-213.

RAMSAY, H., KELLEHER, I., FLANNERY, P., CLARKE, M. C., LYNCH, F., HARLEY, M.,CONNOR, D., FITZPATRICK, C., MORRIS, D. W., & CANNON, M. 2013. Relationship between the COMT-Val158Met and BDNF-Val66Met polymorphisms, childhood trauma and psychotic experiences in an adolescent general population sample. *PLoS ONE*, 8, e79741.

REAGU, S., JONES, R., KUMARI, V. & TAYLOR, P. J. 2013. Angry affect and violence in the context of a psychotic illness: A systematic review and meta-analysis of the literature. *Schizophrenia Research,* 146**,** 46-52.

REES, E., WALTERS, J. T. R., GEORGIEVA, L., ISLES, A. R., CHAMBERT, K. D., RICHARDS, A. L., MAHONEY-DAVIES, G., LEGGE, S. E., MORAN, J. L., MCCARROLL, S. A., O'DONOVAN, M. C., OWEN, M. J. & KIROV, G. 2014.

Analysis of copy number variations at 15 schizophrenia-associated loci. *The British Journal of Psychiatry,* 204**,** 108-114.
ROSENBERG, S., LU, W., MUESER, K., JANKOWSKI, M. & COURNOS, F. 2007. Correlates of adverse childhood events among adults with schizophrenia spectrum disorders. *Psychiatric Services,* 58**,** 245-253.
SARCHIAPONE, M., CARLI, V., CUOMO, C., MARCHETTI, M. & ROY, A. 2009. Assocation between childhood trauma and aggression in male prisoners. *Psychiatry Research,* 165**,** 187-192.
SARTORIUS, N., SHAPIRO, R. & JABLENSKY, A. 1974. The International Pilot Study of Schizophrenia. *Schizophrenia Bulletin,* 1**,** 21-34.
SATO, J. R., DE OLIVEIRA-SOUZA, R., THOMAZ, C. E., BASÍLIO, R., BRAMATI, I. E., AMARO JR, E., TOVAR-MOLL, F., HARE, R. D. & MOLL, J. 2011. Identification of psychopathic individuals using pattern classification of MRI images. *Social Neuroscience,* 6**,** 627-639.
SCHIFFER, B., LEYGRAF, N., MÜLLER, B. W., SCHERBAUM, N., FORSTING, M., WILTFANG, J., GIZEWSKI, E. R. & HODGINS, S. 2013. Structural brain alterations associated with schizophrenia preceded by conduct disorder: A common and distinct subtype of schizophrenia? *Schizophrenia Bulletin,* 39**,** 1115-1128.
SCHIFFER, B., MULLER, B. W., SCHERBAUM, N., HODGINS, S., FORSTING, M., WILTFANG, J., GIZEWSKI, E. R. & LEYGRAF, N. 2011. Disentangling Structural Brain Alterations Associated With Violent Behavior From Those Associated With Substance Use Disorders. *Archives of General Psychiatry,* 68**,** 1039-1049.
SCHIZOPHRENIA WORKING GROUP OF THE PSYCHIATRIC GENOMICS CONSORTIUM 2014. Biological insights from 108 schizophrenia-associated genetic loci. *Nature,* 511**,** 421-427.
SCHUG, R. A., YANG, Y., RAINE, A., HAN, C. & LIU, J. 2010. Structural and psychosocial correlates of birth order anomalies in schizophrenia and homicide. *Journal of Nervous and Mental Disease,* 198**,** 870-875.
SCOTT, S. 2008. An update on interventions for conduct disorder. *Advances in Psychiatric Treatment,* 14**,** 61-70.
SERPER, M. R. 2011. Aggression in schizophrenia. *Schizophrenia Bulletin,* 37**,** 897-898.
SHENTON, M. E., DICKEY, C. C., FRUMIN, M. & MCCARLEY, R. W. 2001. A review of MRI findings in schizophrenia. *Schizophrenia Research,* 49**,** 1-52.
SHEPHERD, A. M., MATHESON, S. L., LAURENS, K. R., CARR, V. J. & GREEN, M. J. 2012. Systematic meta-analysis of insula volume in schizophrenia. *Biological Psychiatry,* 72**,** 775-784.
SHORT, T., THOMAS, S., MULLEN, P. & OGLOFF, J. R. P. 2013. Comparing violence in schizophrenia patients with and without comorbid substance-use disorders to community controls. *Acta Psychiatrica Scandinavica*.
SINGH, J. P., VOLAVKA, J., CZOBOR, P. & VAN DORN, R. A. 2012. A meta-analysis of the Val158Met COMT polymorphism and violent behavior in Schizophrenia. *PLoS ONE,* 7.
SOARES-WEISER, K., MAAYAN, N., BERGMAN, H., DAVENPORT, C., KIRKHAM, A. J., GRABOWSKI, S. & ADAMS, C. E. 2015. First rank symptoms for schizophrenia. *Advances in Psychiatric Treatment,* 21**,** 146-146.
SOYKA, M. 2011. Neurobiology of aggression and violence in schizophrenia. *Schizophrenia Bulletin,* 37**,** 913-920.
STEADMAN, H. J., MULVEY, E. P., MONAHAN, J., ROBBINS, P. C., APPELBAUM, P. S., GRISSO, T., ROTH, L. H. & SILVER, E. 1998. Violence by people discharged from acute psychiatric inpatient facilities and by others in the same neighborhoods. *Archives of General Psychiatry,* 55**,** 393-401.

STEINERT, T., WIEBE, C. & GEBHARDT, R. P. 1999. Aggressive behavior against self and others among first-admission patients with schizophrenia. *Psychiatric Services,* 50**,** 85-90.

STOMPE, T., ORTWEIN-SWOBODA, G. & SCHANDA, H. 2004. Schizophrenia, delusional symptoms, and violence: threat/control-override concept re-examined. *Schizophrenia Bulletin,* 30**,** 31-44.

STROUP, T. S., GERHARD, T., CRYSTAL, S., HUANG, C. & OLFSON, M. 2016. Comparative effectiveness of clozapine and standard antipsychotic treatment in adults with schizophrenia. *American Journal of Psychiatry,* 173**,** 166-173.

STROUS, R., BARK, N., PARSIA, S., VOLAVKA, J. & LACHMAN, H. 1997. Analysis of a functional catechol-O-methyltransferase gene polymorphism in schizophrednia: evidence for association with aggressive and antisocial behaviour. *Psychiatry Research,* 69**,** 71-77.

STROUS, R., NOLAN, K., LAPIDUS, R., DIAZ, L., SAITO, T. & LACHMAN, H. 2003. Aggressive behaviour in schizophrenia is associated with the low enzyme activity COMT polymorphism: a replication study. *American Journal of Medical Genetics,* 120 B**,** 29-34.

STRUCTURAL BRAIN MAPPING GROUP. *VBM8 Toolbox* [Online]. http://dbm.neuro.uni-jena.de/vbm/. [Accessed 31st May 2016].

SULLIVAN, P. F., KENDLER, K. S. & NEALE, M. C. 2003. Schizophrenia as a Complex Trait: Evidence from a Meta-analysis of Twin Studies. *Archives of General Psychiatry,* 60**,** 1187-1192.

SWANSON, J., ESTROFF, S., SWARTZ, M., BORUM, R., LACHICOTTE, W., ZIMMER, C. & WAGNER, R. 1997. Violence and severe mental disorder in clinical and community populations: The effects of psychotic symptoms, comorbidity, and lack of treatment. *Psychiatry,* 60**,** 1-22.

SWANSON, J., SWARTZ, M., VAN DORN, R., ELBOGEN, E., WAGNER, H., ROSENHECK, R., STROUP, T., MCEVOY, J. & LIEBERMAN, J. 2006. A national study of violent behaviour in persons with schizophrenia. *Archives of General Psychiatry,* 63**,** 490-499.

SWANSON, J., VAN DORN, R., SWARTZ, M., SMITH, A., ELBOGEN, E. & MONAHAN, J. 2008. Alternative pathways to violence in persons with schizophrenia: the role of childhood antisocial behaviour problems. *Law and Human Behaviour,* 32**,** 228-240.

SWANSON, J. W., BORUM, R., SWARTZ, M. S. & MONAHAN, J. 1996. Psychotic symptoms and disorders and the risk of violent behaviour in the community. *Criminal Behaviour and Mental Health,* 6**,** 309-329.

TANDON, R., KESHAVAN, M. & NASRALLAH, H. 2008a. Schizophrenia, Just the Facts: What we know in 2008. Epidemiology and etiology. *Schizophrenia Research,* 102**,** 1-18.

TANDON, R., KESHAVAN, M. & NASRALLAH, H. 2008b. Schizophrenia, Just the Facts: What we know in 2008. Overview. *Schizophrenia Research,* 100**,** 4-19.

TANDON, R., NASRALLAH, H. & KESHAVAN, M. 2009. Schizophrenia, Just the Facts. Clinical features and conceptualization. *Schizophrenia Research,* 110**,** 1-23.

TAYLOR, D., PATON, C. & KAPUR, S. 2012. *The Maudsley Prescribing Guidelines in Psychiatry,* London, Wiley-Blackwell.

TENGSTRÖM, A., GRANN, M., LÅNGSTRÖM, N. & KULLGREN, G. 2000. Psychopathy (PCL-R) as a predictor of violent recidivism among criminal offenders with schizophrenia. *Law and Human Behavior,* 24**,** 45-58.

TENGSTRÖM, A., HODGINS, S., GRANN, M., LÅNGSTRÖM, N. & KULLGREN, G. 2004. Schizophrenia and criminal offending: The role of psychopathy and substance use disorders. *Criminal Justice and Behavior,* 31**,** 367-391.

TENGSTROM, A., HODGINS, S. & KULLGREN, G. 2001. Men with schizophrenia who behave violently: the usefulness of an early- versus late-start offender typology. Schizophrenia Bulletin, 27: 205-218. *Schizophrenia Bulletin,* 27**,** 205-218.

TEPLIN, L. A., MCCLELLAND, G. M., ABRAM, K. M. & WEINER, D. A. 2005. Crime victimization in adults with severe mental illness: Comparison with the national crime victimization survey. *Archives of General Psychiatry,* 62**,** 911-921.

TOSATO, S., BONETTO, C., DI FORTI, M., COLLIER, D., CRISTOFALO, D., BERTANI, M., ZANONI, M., MARRELLA, G., LAZZAROTTO, L., LASALVIA, A., DE GIRONCOLI, M., TANSELLA, M., DAZZAN, P., MURRAY, R. & RUGGERI, M. 2011. Effect of COMT genotype on aggressive behaviour in a community cohort of schizophrenic patients. *Neuroscience Letters,* 495**,** 17-21.

TROST, S., PLATZ, B., USHER, J., SCHERK, H., WOBROCK, T., EKAWARDHANI, S., MEYER, J., REITH, W., FALKAI, P. & GRUBER, O. 2013. DISC1 (disrupted-in-schizophrenia 1) is associated with cortical grey matter volumes in the human brain: A voxel-based morphometry (VBM) study. *Journal of Psychiatric Research,* 47**,** 188-196.

TURNER, J. A., CALHOUN, V. D., MICHAEL, A., VAN ERP, T. G. M., EHRLICH, S., SEGALL, J. M., GOLLUB, R. L., CSERNANSKY, J., POTKIN, S. G., HO, B. C., BUSTILLO, J., SCHULZ, S. C. & WANG, L. 2012. Heritability of multivariate gray matter measures in schizophrenia. *Twin Research and Human Genetics,* 15**,** 324-335.

TYRER, P., COOPER, S., HERBERT, E., DUGGAN, C., CRAWFORD, M., JOYCE, E., RUTTER, D., SEIVEWRIGHT, H., O'SULLIVAN, S., RAO, B., CICCHETTI, D. & MADEN, T. 2007. The quantification of violence scale: A simple method of recording significant violence. *International Journal of Social Psychiatry,* 53**,** 485-497.

ULLRICH, S., KEERS, R. & COID, J. 2014. Delusions, anger and serious violence: new findings from the MacArthur Violence Risk Assessment Study. *Schizophrenia Bulletin,* 40**,** 1174-1181.

VAN DONGEN, J., BUCK, N. & VAN MARLE, H. 2014. Unravelling offending in schizophrenia: Factors characterising subgroups of offenders. *Criminal Behaviour and Mental Health*.

VAN DONGEN, J. D. M., BUCK, N. M. L., BARENDREGT, M., VAN BEVEREN, N. M., DE BEURS, E. & VAN MARLE, H. J. C. 2015. Anti-social personality characteristics and psychotic symptoms: Two pathways associated with offending in schizophrenia. *Criminal Behaviour and Mental Health,* 25**,** 181-191.

VAN DONGEN, J. D. M., BUCK, N. M. L. & VAN MARLE, H. J. C. 2012. Delusional distress partly explains the relation between persecutory ideations and inpatient aggression on the ward. *Psychiatry Research,* 200**,** 779-783.

VAN DORN, R., VOLAVKA, J. & JOHNSON, N. 2012. Mental disorder and violence: Is there a relationship beyond substance use? *Social Psychiatry and Psychiatric Epidemiology,* 47**,** 487-503.

VAN ERP, T. G. M., HIBAR, D. P., RASMUSSEN, J. M., GLAHN, D. C., PEARLSON, G. D., ANDREASSEN, O. A., AGARTZ, I., WESTLYE, L. T., HAUKVIK, U. K., DALE, A. M., MELLE, I., HARTBERG, C. B., GRUBER, O., KRAEMER, B., ZILLES, D., DONOHOE, G., KELLY, S., MCDONALD, C., MORRIS, D. W., CANNON, D. M., CORVIN, A., MACHIELSEN, M. W. J., KOENDERS, L., DE HAAN, L., VELTMAN, D. J., SATTERTHWAITE, T. D., WOLF, D. H., GUR, R. C., GUR, R. E., POTKIN, S. G., MATHALON, D. H., MUELLER, B. A., PREDA, A., MACCIARDI, F., EHRLICH, S., WALTON, E., HASS, J., CALHOUN, V. D., BOCKHOLT, H. J., SPONHEIM, S. R., SHOEMAKER, J. M., VAN HAREN, N. E. M., POL, H. E. H., OPHOFF, R. A., KAHN, R. S., ROIZ-SANTIAEZ, R., CRESPO-FACORRO, B., WANG, L., ALPERT, K. I., JÖNSSON, E. G., DIMITROVA, R., BOIS, C., WHALLEY, H. C., MCINTOSH, A. M., LAWRIE, S. M., HASHIMOTO, R., THOMPSON, P. M. & TURNER, J. A. 2016. Subcortical brain volume abnormalities in 2028 individuals with schizophrenia and 2540 healthy controls via the ENIGMA consortium. *Molecular Psychiatry,* 21**,** 547-553.

VAN HAREN, N. E. M., SCHNACK, H. G., KOEVOETS, M. G. J. C., CAHN, W., HULSHOFF POL, H. E. & KAHN, R. S. 2016. Trajectories of subcortical volume change in schizophrenia: A 5-year follow-up. *Schizophrenia Research,* 173**,** 140-145.

VAN OS, J., RUTTEN, B. P., MYIN-GERMEYS, I., DELESPAUL, P., VIECHTBAUER, W., VAN ZELST, C., BRUGGEMAN, R., REININGHAUS, U., MORGAN, C., MURRAY, R. M., DI FORTI, M., MCGUIRE, P., VALMAGGIA, L. R., KEMPTON, M. J., GAYER-ANDERSON, C., HUBBARD, K., BEARDS, S., STILO, S. A., ONYEJIAKA, A., BOURQUE, F., MODINOS, G., TOGNIN, S., CALEM, M., O'DONOVAN, M. C., OWEN, M. J., HOLMANS, P., WILLIAMS, N., CRADDOCK, N., RICHARDS, A., HUMPHREYS, I., MEYER-LINDENBERG, A., LEWEKE, F. M., TOST, H., AKDENIZ, C., ROHLEDER, C., BUMB, J. M., SCHWARZ, E., ALPTEKIN, K., ÜÇOK, A., SAKA, M. C., ATBAGOĞLU, E. C., GÜLÖKSÜZ, S., GUMUS-AKAY, G., CIHAN, B., KARADAĞ, H., SOYGÜR, H., CANKURTARAN, E. S., ULUSOY, S., AKDEDE, B., BINBAY, T., AYER, A., NOYAN, H., KARADAYI, G., AKTURAN, E., ULAŞ, H., ARANGO, C., PARELLADA, M., BERNARDO, M., SANJUÁN, J., BOBES, J., ARROJO, M., SANTOS, J. L., CUADRADO, P., SOLANO, J. J. R., CARRACEDO, A., BERNARDO, E. G., ROLDÁN, L., LÓPEZ, G., CABRERA, B., CRUZ, S., MESA, E. M. D., POUSO, M., JIMÉNEZ, E., SÁNCHEZ, T., RAPADO, M., GONZÁLEZ, E., MARTÍNEZ, C., SÁNCHEZ, E., OLMEDA, M. S., DE HAAN, L., VELTHORST, E., VAN DER GAAG, M., SELTEN, J. P., VAN DAM, D., VAN DER VEN, E., VAN DER MEER, F., MESSCHAERT, E., KRAAN, T., BURGER, N., LEBOYER, M., SZOKE, A., SCHÜRHOFF, F., LLORCA, P. M., JAMAIN, S., TORTELLI, A., FRIJDA, F., VILAIN, J., GALLIOT, A. M., BAUDIN, G., FERCHIOU, A., et al. 2014. Identifying gene-environment interactions in schizophrenia: Contemporary challenges for integrated, large-scale investigations. *Schizophrenia Bulletin,* 40**,** 729-736.

VAN WINKEL, R., HENQUET, C., ROSA, A., PAPIOL, S., FAÑANÁS, L., DE HERT, M., PEUSKENS, J., VAN OS, J. & MYIN-GERMEYS, I. 2008. Evidence that the COMTVal158Met polymorphism moderates sensitivity to stress in psychosis: An experience-sampling study. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics,* 147**,** 10-17.

VARESE, F., SMEETS, F., DRUKKER, M., LIEVERSE, R., LATASTER, T., VIECHTBAUER, W., READ, J., VAN OS, J. & BENTALL, R. P. 2012. Childhood adversities increase the risk of psychosis: A meta-analysis of patient-control, prospective-and cross-sectional cohort studies. *Schizophrenia Bulletin,* 38**,** 661-671.

VASSOS, E., PEDERSEN, C. B., MURRAY, R. M., COLLIER, D. A. & LEWIS, C. M. 2012. Meta-analysis of the association of urbanicity with schizophrenia. *Schizophrenia Bulletin,* 38**,** 1118-1123.

VILLODAS, M. T., LITROWNIK, A. J., THOMPSON, R., JONES, D., ROESCH, S. C., HUSSEY, J. M., BLOCK, S., ENGLISH, D. J. & DUBOWITZ, H. 2014. Developmental transitions in presentations of externalizing problems among boys and girls at risk for child maltreatment. *Development and Psychopathology,* 27**,** 205-219.

VITA, A., DE PERI, L., DESTE, G., BARLATI, S. & SACCHETTI, E. 2015. The Effect of Antipsychotic Treatment on Cortical Gray Matter Changes in Schizophrenia: Does the Class Matter? A Meta-analysis and Meta-regression of Longitudinal Magnetic Resonance Imaging Studies. *Biological Psychiatry,* 78**,** 403-412.

VOLAVKA, J. 2014. Comorbid personality disorders and violent behavior in psychotic patients. *Psychiatric Quarterly,* 85**,** 65-78.

VOLAVKA, J. & CITROME, L. 2011. Pathways to aggression in schizophrenia affect results of treatment. *Schizophrenia Bulletin,* 37**,** 921-929.

VOLAVKA, J., LASKA, E., BAKER, S., MEISNER, M., CZOBOR, P. & KRIVELEVICH, I. 1997. History of violent behaviour and schizophrenia in different cultures.

Analyses based on the WHO study on determinants of outcome of severe mental disorders. *British Journal of Psychiatry,* 170**,** 9-14.
WAHLBECK, K., CHEINE, M., ESSALI, A. & ADAMS, C. 1999. Evidence of clozapine's effectiveness in schizophrenia: A systematic review and meta-analysis of randomized trials. *American Journal of Psychiatry,* 156**,** 990-999.
WALSH, E., BUCHANAN, A. & FAHY, T. 2002. Violence and schizophrenia: examining the evidence. *British Journal of Psychiatry,* 180**,** 490-495.
WEBSTER, C., DOUGLAS, K., EAVES, D. & HART, S. 1997. *HCR-20: Assessing risk for violence (version 2),* Vancouver, Simon Fraser University.
WEISS, E. 2012. Neuroimaging and neruocognitive correlates of aggression and violence in schizophrenia. *Scientifica* [Online]. [Accessed 13/12/2012].
WEISZ, J., HAWLEY, K. & DOSS, A. 2004. Empirically tested psychotherapies for youth internalizing and externalizing problems and disorders. *Child and Adolescent Psychiatric Clinics of North America,* 13**,** 729-815.
WELLCOME TRUST CENTRE FOR NEUROIMAGING. *SPM8* [Online]. http://www.fil.ion.ucl.ac.uk/spm/. [Accessed 31st May 2016].
WITT, K., VAN DORN, R. & FAZEL, S. 2013. Risk Factors for Violence in Psychosis: Systematic Review and Meta-Regression Analysis of 110 Studies. *PLoS ONE,* 8.
WORLD HEALTH ORGANIZATION 1992. *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines,* Geneva, World Health Organization.
WRIGHT, I. C., RABE-HESKETH, S., WOODRUFF, P. W. R., DAVID, A. S., MURRAY, R. M. & BULLMORE, E. T. 2000. Meta-analysis of regional brain volumes in schizophrenia. *American Journal of Psychiatry,* 157**,** 16-25.
YALE BIOIMAGE SUITE PACKAGE. http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html. [Accessed 31st May 2016].
YANG, Y. & RAINE, A. 2009. Prefrontal structural and functional brain imaging findings in antisocial, violent, and psychopathic individuals: a meta-analysis. *Psychiatry Research: Neuroimaging,* 174**,** 81-88.
YANG, Y., RAINE, A., HAN, C., SCHUG, R., TOGA, A. & NARR, K. 2010. Reduced hippocampal and parahippocampal volumes in murderers with schizophrenia. Psychiatry Research: Neuroimaging, 182: 9-13. *Psychiatry Research: Neuroimaging,* 182**,** 9-13.
YANG, Y., RAINE, A., NARR, K., COLLETTI, P. & TOGA, A. 2009. Localization of deformations within the amygdala in individuals with psychopathy. *Archives of General Psychiatry,* 66**,** 986-994.
YAO, L., LUI, S., LIAO, Y., DU, M. Y., HU, N., THOMAS, J. A. & GONG, Q. Y. 2013. White matter deficits in first episode schizophrenia: An activation likelihood estimation meta-analysis. *Progress in Neuro-Psychopharmacology and Biological Psychiatry,* 45**,** 100-106.
YU, R., GEDDES, J. R. & FAZEL, S. 2012. Personality disorders, violence, and antisocial behavior: A systematic review and meta-regresion analysis. *Journal of Personality Disorders,* 26**,** 775-792.
YUDOFSKI, S., SILVER, J., JACKSON, W., ENDICOTT, J. & WILLIAMS, D. 1986. The Overt Aggression Scale for the objective rating of verbal and physical aggression. *American Journal of Psychiatry,* 143**,** 35-39.
ZAMMIT, S., ALLEBECK, P., ANDREASSON, S., LUNDBER, I. & LEWIS, G. 2002. Self-report cannabis use as a risk factor for schizophrenia in Swedish conscripts of 1969: historical cohort study. *British Medical Journal* 325**,** 1199.
ZAMMIT, S., JONES, G., JONES, S., NORTON, N., SANDERS, R., MILHAM, C., MCCARTHY, G., JONES, L., CARDNO, A., GRAY, M., MURPHY, K., O'DONOVAN, M. & OWEN, M. 2004. Polymorphisms in the MAOA, MAOB, and COMT genes and aggressive behaviour in schizophrenia. . *American Journal of Medical Genetics,* 128B**,** 19-20.

ZAMMIT, S., SPURLOCK, G., WILLIAMS, H., NORTON, N., WILLIAMS, N., O'DONOVAN, M. C. & OWEN, M. J. 2007. Genotype effects of CHRNA7, CNRI and COMT in schizophrenia: Interactions with tobacco and cannabis use. *British Journal of Psychiatry,* 191**,** 402-407.

Appendix A. Ethical Approval

National Research Ethics Service
Birmingham, East, North and Solihull Research Ethics Committee
REC Offices
Prospect House
Fishing Line Road
Enfield
Redditch
B97 6EW

Telephone: 01527 582534
Facsimile: 01527 582540

17 December 2010

Professor Declan Murphy
Head of Department of Forensic and Neurodevelopment Sciences
Kings College London
Institute of Psychiatry, Box PO50
De Crespigny Park
Denmark Hill
London
SE5 8AF

Dear Professor Murphy

Study Title:	**Identifying markers to predict violence in schizophrenia.**
REC reference number:	**10/H1206/80**
Protocol number:	**CSA/10/037**

Thank you for your letter of 01 December 2010, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information was considered in correspondence by a sub-committee of the REC. A list of the sub-committee members is attached.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

The Committee has not yet been notified of the outcome of any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as

one Research Ethics Committee has notified the outcome of a SSA. In the meantime no study procedures should be initiated at non-NHS sites.

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

For NHS research sites only, management permission for research ("R&D approval") should be obtained from the relevant care organisation(s) in accordance with NHS research governance arrangements. Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where the only involvement of the NHS organisation is as a Participant Identification Centre (PIC), management permission for research is not required but the R&D office should be notified of the study and agree to the organisation's involvement. Guidance on procedures for PICs is available in IRAS. Further advice should be sought from the R&D office where necessary.

Sponsors are not required to notify the Committee of approvals from host organisations.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		21 October 2010
Investigator CV		26 August 2009
Response to Request for Further Information		01 December 2010
Participant Information Sheet: Birmingham and Solihull Mental Health Foundation Trust	2	01 December 2010
Protocol	1	05 October 2010
Participant Information Sheet: St Andrew's Healthcare	2	01 December 2010
REC application	IRAS 3.0	21 October 2010
Participant Information Sheet: Northamptonshire Healthcare Foundation Trust	2	01 December 2010
Participant Consent Form: Consent Form	1	04 August 2010
Participant Consent Form: Consent Form for Police and Court Records		04 August 2010
Participant Information Sheet: Healthy Participant Information Sheet	2	01 December 2010
Participant Information Sheet: MRI Information Sheet	2	01 December 2010
Project Planner	1	11 August 2010
Scientific Review		26 January 2010

Heart of England Hub
Mental Health Research Network

Birmingham and Solihull NHS
Mental Health NHS Foundation Trust

Research & Development Unit
Suite O
Radclyffe House
66/68 Hagley Road
Edgbaston
Birmingham
B16 8PF

Tel: 0121 678 4327
Fax: 0121 678 4319

Professor Declan Murphy
Department of Forensic and Neurodevelopment Sciences
Kings College London
Institute of Psychiatry
London
SE5 8AF

8th August 2011

Dear Professor Murphy

Re: Identifying markers to predict violence in schizophrenia

Thank you for providing us with the documentation to support your application for R&D approval. This research was approved by the Director of Research & Development and we have received notification of a favourable ethical opinion. You may therefore commence the work.

Please note that the Trust's approval of this research is given on the understanding that you are aware of and will fulfil your responsibilities under the Department of Health's *Research Governance Framework for Health and Social Care*, including complying with any monitoring/auditing of research undertaken by the Research & Development Unit.

In particular, whilst conducting your study you should respect the confidentiality of data obtained from participants.

Please do not hesitate in contacting the Research & Development Unit should you require any advice or support on any aspect of your project. When contacting us it would be helpful to quote our reference number for this project: **NRR 1065.**

Yours sincerely

Max Birchwood
Director of Research and Development

Research Support Service
Community, Mental Health & Learning Disability Services

Leicestershire Partnership NHS
NHS Trust
A University Teaching Trust

FINAL APPROVAL (SPONSOR INDEMNITY)

Research & Development Office
Lakeside House
4 Smith Way
Grove Park
Enderby
Leicester
LE19 1SS

Direct dial: 0116 295 7641
Email: david.clarke@leicspart.nhs.uk

Tel: 0116 295 7500
Fax: 0116 295 7599
Web: www.leicspt.nhs.uk

DC/ADMH0592/Mu-Oa-Ha-Ki/Permission

Professor Declan Murphy
c/o Miss Stephanie Harris
2/24 The Braye Centre,
St. Andrews Healthcare,
Northampton
NN1 5BW

17th September 2012

Dear Miss Harris

RE: Identifying Markers to Predict Violence in Schizophrenia

Thank you for applying for NHS Permission (also known as Research Governance Approval) for the above-named study. I am pleased to inform you that the formal review of the project is now complete. The outcome of this review is given below:

Full Approval	☒	Approval in Principle	☐	Approval refused	☐

Your responsibilities are set out in the attached agreement, which must be signed and returned to the Research Office. You should keep a copy for your records. All research must be managed in accordance with the requirements of the Dept. of Health Research Governance Framework (RGF), and to ICH-GCP standards. In order to ensure compliance with these standards, the Trust may randomly select your study for audit against these standards at any time, and may employ an external agency for this purpose. This approval is contingent upon the validity of the following information:

Study Summary			
Chief Investigator (Supervisor):	Professor Declan Murphy {Institute of Psychiatry}	HC/(LoA)[1]	Yes/No
Principal Investigator:	Miss Stephanie Harris {Kings College London}	(HC)/LoA	Yes/No
Investigator (Other)	Dr Clare Oakley {Kings College London}	(HC)/LoA	Yes/No
Investigator (Other)	Dr. Daniel Kinnair {LPT}	HC/LoA	Yes/No/NA
Indemnity Provider:	Zurich Municipal Employers & Public Liability		
Sponsor	Kings College London		
NIHR Portfolio:	NO		
Qualification	PhD Forensic & Neurodevelopmental Sciences		
Start Date: 01/06/2012	End Date: 31/05/2013		
Recruitment Target	30		

Approved Documentation		
Notice of Amendment 4	56840/291795/13/333/11318	9th February 2012
Leicestershire SSI Form	56840/323534/6/444/136322 /243687	9th February 2012
Consent Form	Version 3	9th February 2012
MRI Information Sheet	Version 3	9th February 2012
Positive & Negative Symptoms Scale (PANSS)		
CV: Clare Oakley		5th September 2011
CV: Stephanie Harris		24th April 2012
CV: Professor Declan Murphy		26th August 2009

[1] Honorary Contract or Letter of Access

Northamptonshire Healthcare NHS
NHS Foundation Trust

Research and Development
Sudborough House,
St. Mary's Hospital,
London Road,
Kettering,
Northamptonshire,
NN15 7PW

Direct Dial: (01536) 494756
Fax No: (01536) 494216

Associate Medical Director: Dr Sean Scanlon

Head of Quality Support and Assurance: David Thomas

R&D Facilitator: Ann Fountain

9 December 2011

Professor Declan Murphy
Head of Department of Forensic and Neurodevelopment Sciences
Kings College London
Institute of Psychiatry, Box PO50
De Crespigny Park
Denmark Hill
London SE5 8AF

Dear Professor Murphy

Ref: **10/H1206/80**
Title: **Identifying markers to predict violence in schizophrenia**
Project Status: **Approved**
End Date: **01/03/2015**

I am pleased to confirm that with effect from the date of this letter, the above study now has Trust Research & Development permission to commence at Northamptonshire Healthcare NHS Foundation Trust.

All documents received by this office have been reviewed and form part of the approval. The documents received and approved are as follows:

Document Name	Version	Valid to Date
Covering Letter		21.10.10
Investigator CV		26.08.09
Response to Request for further information		01.12.10
Protocol	1	05.10.10
REC application	IRAS 3.0	21.10.10
Participant Information Sheet: Northamptonshire Healthcare Foundation Trust	2	01.12.10
Participant Consent form: Consent Form	1	04.08.10

Oxford Health NHS
NHS Foundation Trust

Professor John Geddes
Research & Development Lead
Dept of Psychiatry, University of Oxford
Warneford Hospital
Oxford OX3 7JX
Tel: 01865 226451 Fax: 01865 204198
e-mail: john.geddes@psych.ox.ac.uk

Our Ref: OxH 912

28 May 2012

Dr E Vassos
Consultant Psychiatrist
Oxford Health NHS FT
South East Buckinghamshire CMHT
Haleacre Unit, Amersham Hospital
Amersham, HP7 OJD

Dear Dr Vassos

Re: Identifying markers to predict violence in schizophrenia
REC No. 10/H1206/80

I am pleased to confirm that Oxford Health NHS Foundation Trust will grant NHS Permission (management approval) for this research study until the study end date of 1 July 2015, as described in your application to the National Research Ethics Service. NHS Permission is granted as of the date of this letter. This confirmation is dependent on the formal approval of the National Research Ethics Service and any other relevant regulatory body.

I must remind you of the declaration that was signed in the Site-Specific Information form. This explains your responsibilities as a researcher including adherence to the principles of the Research Governance Framework (RGF), Good Clinical Practice (GCP) and the Data Protection Act. Please note that the Trust is required to monitor research to ensure compliance with the RGF and other legal and regulatory requirements. This is achieved by random audit of research.

NHS Permission is dependent upon completion and submission of satisfactory annual reports. It is a condition of NHS Permission that you inform the Trust R&D department of any amendments to the conduct of the study and provide a final report on completion of the study.

I wish you every success with the study

Yours sincerely

Professor John Geddes
Research & Development Lead Director

National Research Ethics Service
Birmingham, East, North and Solihull Research Ethics Committee
REC Offices
Prospect House
Fishing Line Road
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06 April 2011

Professor Declan Murphy
Institute of Psychiatry, Box PO50
De Crespigny Park
London
SE5 8AF

Dear Professor Murphy

Study title:	**Identifying markers to predict violence in schizophrenia.**
REC reference number:	**10/H1206/80**
SSA reference number:	**11/EM/0111**
Protocol number:	**CSA/10/037**

The REC gave a favourable ethical opinion to this study on 17.12.2010.

Notification(s) have been received from local assessor(s), following site-specific assessment. On behalf of the Committee, I am pleased to confirm the extension of the favourable opinion to the new site(s) and investigator(s) listed below:

Research Site	Principal Investigator / Local Collaborator
St Andrews Healthcare, Billing Road, Northampton, Northamptonshire, NN1 5DG (Clinical/neuropsychological interviews, blood sample)	Dr Marco Picchioni

The favourable opinion is subject to management permission or approval being obtained from the host organisation prior to the start of the study at the site concerned.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

Appendix B. Alcohol and Drugs Questionnaire

St Andrew's Academic Centre

Institute of Psychiatry at The Maudsley | KING'S College LONDON University of London | St Andrew's HEALTHCARE

Alcohol and Drugs Questionnaire

Participant ID: .....

Date of Completion: ..... / ..... / .....

Please answer the questions below as accurately as you can.

1. Alcohol

a. Have you ever drunk alcohol? Yes ☐ No ☐

(If you answer no go straight to question 2)

b. What age did you first drink? ☐

c. How often did you drink alcohol before the age of 15?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

d. How often did you drink alcohol between the ages of 15 and 18?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

e. How often do you currently have a drink containing alcohol?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

(If you answer never go straight to question 2)

f. How many units of alcohol do you have on a typical day when you are drinking?

i. 1 or 2	☐	v. 10 to 14	☐
ii. 3 or 4	☐	vi. 15 to 19	☐
iii. 5 or 6	☐	vii. 20 to 29	☐
iv. 7 to 9	☐	viii. 30 or more	☐

Units of alcohol

1 single measure of spirits or a small glass of wine = 1 unit

1 standard pint of beer or lager = 2 units

1 pint of strong lager = 3 units

g. How often do you have six or more units on one occasion?

i. Never	☐	iv. Weekly	☐
ii. Less than monthly	☐	v. Daily or almost daily	☐
iii. Monthly	☐		

h. Have you ever been cautioned, arrested or convicted for a drink related offence? e.g. drink driving or drunk and disorderly

Yes ☐ No ☐

i. Have you ever stolen to buy alcohol? Yes ☐ No ☐

j. Have you ever been violent when drunk? Yes ☐ No ☐

k. Have you ever been the victim of violence when drunk?

Yes ☐ No ☐

2. Cannabis

a. Have you ever used cannabis? Yes ☐ No ☐

(If you answer no go straight to question 3)

b. What age did you first use? ☐

c. How often did you use cannabis before the age of 15?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

d. How often did you use cannabis between the ages of 15 and 18?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

e. How often do you currently use cannabis?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

(If you answer never go straight to question 3)

f. What type of cannabis do you use?

i. Hash (cannabis resin/solid) ☐
ii. Imported herbal cannabis ☐
iii. Skunk / sensimilla ☐
iv. Super skunk ☐

g. How much do you use on average per day?

i. Less than 1 joint ☐
ii. 1 joint ☐
iii. 2 or 3 joints ☐
iv. 4 or more joints ☐

3. Cocaine / crack cocaine

a. Have you ever used cocaine or crack cocaine? Yes ☐ No ☐

(If you answer no go straight to question 4)

b. What age did you first use? ☐

c. How often did you use cocaine before the age of 15?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

d. How often did you use cocaine between the ages of 15 and 18?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

e. How often do you currently use cocaine?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

4. Heroin / opiates

a. Have you ever used heroin? Yes ☐ No ☐

(If you answer no go straight to question 5)

b. What age did you first use? ☐

c. How often did you use heroin before the age of 15?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

d. How often did you use heroin between the ages of 15 and 18?

i. Never ☐ iv. 2-3 times per week ☐

ii. Monthly or less ☐ v. 4 or more times per week ☐

iii. 2-4 times per month ☐

e. How often do you currently use heroin?

i. Never ☐ iv. 2-3 times per week ☐

ii. Monthly or less ☐ v. 4 or more times per week ☐

iii. 2-4 times per month ☐

(If you answer never go straight to question 5)

f. Do you inject? Yes ☐ No ☐

g. How much do you use on average per day?

i. Less than half a gram ☐

ii. Between half a gram and a gram ☐

iii. More than a gram ☐

5. Amphetamines

a. Have you ever used amphetamines? Yes ☐ No ☐

(If you answer no go straight to question 6)

b. What age did you first use? ☐

c. How often did you use amphetamines before the age of 15?

i. Never ☐ iv. 2-3 times per week ☐

ii. Monthly or less ☐ v. 4 or more times per week ☐

iii. 2-4 times per month ☐

d. How often did you use amphetamines between the ages of 15 and 18?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

e. How often do you currently use amphetamines?

i. Never ☐
ii. Monthly or less ☐
iii. 2-4 times per month ☐
iv. 2-3 times per week ☐
v. 4 or more times per week ☐

6. Other

a. Please list any other drugs you have used regularly (e.g. illicit benzodiazepines).

i. _____
ii. _____
iii. _____

b. Have you ever been cautioned, arrested or convicted for a drug related offence? e.g. possession or intent to supply

Yes ☐ No ☐

c. Have you ever stolen to buy drugs? Yes ☐ No ☐

d. Have you ever been violent when under the influence of drugs?

Yes ☐ No ☐

e. Have you ever been the victim of violence when under the influence of drugs? Yes ☐ No ☐